

Rudolph Matas, 1860–1957

Rudolph Matas was the first to use spinal anesthesia clinically. In 1902, he devised a "radical" operation for aneurysm, "aneurysmorrhaphy" which was the first advance in this type of surgery since the days of John Hunter He was an able teacher, a clear and original thinker and tireless investigator. He maintained an active interest in his work up to a few years prior to his death at 97 years of age. He was the first to close an arteriovenous fistula between the carotid artery and the jugular vein (1912). In his Bigelow address in 1927 he summarized the qualities that make a great surgeon, and in this summary he reflected his own image, "The surgeon must be original He must be endowed with the spirit of invention; he must possess a faculty for investigation, or that spontaneous intuition which leads a man to seek untrodden paths and discover new truths, new methods, new procedures or forge new and unknown weapons to battle with disease or stay the hand of death."

Peripheral Vascular Diseases

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AN OBJECTIVE APPROACH

By

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With a Foreword by

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"Nature is written in mathematical symbols." GALILEO, 1564–1642

It is
with grateful appreciation
that this book is dedicated
to my family

Betty, David, Susan
Wiley and Mabel

Foreword

During a considerable period of years, it has been my privilege and pleasure to observe the work of DR. TRAVIS WINSOR as a teacher, clinical and experimental investigator, as well as an active practitioner.

In addition to his teaching program in the School of Medicine at the University of Southern California, he continued to pursue investigations of the peripheral vascular system, which attracted the cooperation, assistance, and support of numerous individuals, both laymen and professional.

The techniques used in this work ranged from the most simple, but wise and accurate observations, to the use of the most complicated instruments available for such studies today.

Through these efforts, there has been an accumulation of knowledge that constitutes the background of this book. The interpretations of findings, as well as the methods of diagnosis and treatment are of great value and inspiration to students, teachers, investigators and practitioners who are especially interested in the peripheral vascular system, and its related conditions.

The great efforts and time expended in the preparation of the manuscript and illustrations are justified in its presentation to the entire scientific medical world.

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Preface

Rapid advances in the understanding, diagnosis and treatment of abnormalities of the peripheral circulation have occurred during the past decade during which a new era has been entered, that of electronic instrumentation. The development of instruments which provide objective measurements to augment and, in some cases, to take the place of previous subjective observations has given great impetus to the study of the circulation of blood through the extremities.

Five great eras can be recognized in the development of our knowledge of the peripheral circulation. These are the eras of: (1) observation of the living; (2) dissection of the dead; (3) physiologic investigation; (4) application of optics, mathematics and physics, and (5) application of electronics. The first era began with Hippocrates, 460 B.C. to 377 B.C., who recognized and described gangrene and the effects of other peripheral vascular diseases. The second era began at the time of Leonardo De Vinci, 1452 to 1515, who noticed while dissecting that the arteries of the young were elastic and straight and those of the old were thick, rigid and tortuous. The third era began with William Harvey, 1578 to 1657, who established the scientific method for physiologic investigation and showed that blood circulated in a closed system of vessels. The fourth era occurred at the time of Antony van Leeuwenhoek, 1632 to 1723, and J L. Poiseuille, 1799 to 1869, with the development of optics, mathematics and physics. Van Leeuwenhoek was the first to use the microscope for the systematic study of the blood vessels. Poiseuille used mathematics to describe the factors which control the flow of blood in vessels The fifth era is that of electronics which began with the development of the vacuum tube by DeForest and is continuing to grow and expand with more and greater advances yearly.

These developments have made possible numerous instruments for the objective measurements of the peripheral circulation.

The purpose of this monograph is to present through these improved instruments an objective approach to the understanding and treatment of patients with peripheral vascular disease. This must start with a knowledge of the functional anatomy of the human circulation and nervous system and an understanding of the way in which the various organs of the body affect blood flow. Important aspects of the physical examination of the vascular system are considered in the light of various objective studies with emphasis placed on the plethysmographic examination which is a practical and informative laboratory examination and making possible objective observations of the peripheral circulation not obtainable in various other studies The information gained from these studies is important in understanding disease, determining treatment and making comparisons of various pharmacologic agents, physical therapeutic and surgical procedures

The various therapeutic measures employed in the field of peripheral vascular disease which have been found useful by the author are discussed in detail Great advances have been made in the surgical treatment of peripheral vascular diseases in the form of thromboendarterectomy, arterial grafts and reconstructive surgery. Advanced instrumentation has made it possible for the internist and surgeon to advance together.

In the writing of this manuscript the immeasurable help which has been received from numerous friends is gratefully acknowledged.

Sincere appreciation is expressed to the Los Angeles County and Ventura County Heart Associations which supported many of the original studies presented. Especially important is the outstanding help of Lewis T Bullock, M.D, Chairman of the Research Committee of the Los Angeles County Heart Association, who forcefully has shown the need for original investigation in the West and whose continued efforts have made possible funds and facilities for our own work and for the work of innumerable other investigators. From his initial ideas and efforts there has grown an ever enlarging research effort in this area. The generous help of Charles Hufnagle, M D, made possible the establishment

of the Los Angeles County Heart Association Artery Bank which is described.

The encouragement initially provided by B. O. Raulston, M.D., Dean Emeritus of the University of Southern California, and the long, stimulating and pleasant association with George E. Burch, M.D, Professor of Medicine, Tulane University, New Orleans, Louisiana, have been important factors in the continuance of the studies reported in this monograph. Many of these studies were carried out with facilities provided by the Hospital of the Good Samaritan, Los Angeles and the cooperation of the Hospital Administration is gratefully acknowledged. The exchange of ideas and the stimulating discussions held frequently with Chester Hyman, Ph D., Professor of Physiology, University of Southern California School of Medicine have been especially rewarding and have been a source of renewed enthusiasm. Wilbur A. Selle, M.D., Professor of Biophysics, University of California at Los Angeles, School of Medicine, assisted in getting this manuscript underway. Invaluable mathematical assistance was provided through E. K. Fisher of Lockheed Aircraft Missile Systems Division J. Howard Payne, M D, provided aortograms and performed many of the surgical procedures. Harold Karpman, M.D., National Heart Institute Trainee and Thomas Berne, Heart Research Fellow have given valued editorial and technical assistance.

The art work was executed by Gregg Moris and Alan Cole whose abilities have transformed many an ordinary sketchy outline into an attractive illustration. Manuel Gonzales assisted with these illustrations. The most continuous work of the book, the typing and retyping of the manuscript, has been done primarily by my most capable secretary, Mrs Sally Cody. She has had the assistance of Miss Doris Wade.

It is hoped that this book will give a fresh approach to the study of peripheral vascular disease and will stimulate a closer association between basic scientists and physicians from which will evolve new and better instruments for the objective measurements of the peripheral circulation.

MECHANISMS OF HYPERTENSION

Chapter I

THE COMPLEX OF FACTORS IN THE HUMAN DISEASE

INTRODUCTION

ARTERIAL hypertension is only a sign of disturbed hemodynamics. At the basis of this disturbance is generalized vasospasm. Without vasospasm the diastolic blood pressure would not rise significantly (1).

Generalized vasospasm is a condition common to a number of hemodynamic disturbances. Whenever effective blood flow through vital organs is reduced, a series of reactions is set in motion aimed at restoring flow through those organs at the expense of other less essential ones. Thus, vasospasm follows hemorrhage, precedes and accompanies shock, severe coronary occlusion, heart failure and other states of circulatory embarrassment. It even accompanies the upright position to a small degree. In these conditions blood pressure is normal or low and effective circulating blood volume and cardiac output low, the vasospasm accompanying the reduction in circulation. Only in late, "irreversible" stages of shock is vasospasm replaced by vasodilatation or its capillary counterparts. If the peripheral circulatory state of vasospasm remained constant, and effective circulating blood volume or cardiac output were returned to normal, hypertension would ensue.

Therefore, when generalized vasospasm occurs in the presence of a normally functioning heart, a normal blood volume and a normal blood viscosity (dependent on the

blushed rather widely over her face, neck and shoulders (there were blotches) when he examined her heart. She appeared a bit timorous and tense, but under good self-control. Her axillae were wet (or would have been, had she not used antisweating preparations) and her hands and feet were cold and moist. She admitted blushing easily in the past on the least provocation. She was excessively neat, regular in her habits, almost compulsive but quite unassertive. Laboratory examinations were unrevealing. Being curious, he immersed her hand in ice water for 1 minute, a painful experience; she showed no emotion but her blood pressure rose to 168/99 mm. Hg, falling in 5 minutes to lower levels after it was removed.

This young woman's vascular response to the stress of an examination and to the pain of ice water was almost certainly mediated through the sympathetic nervous system. She was one of those individuals, very common in the population, who react to stress by vasospasm. Her blushing was characteristic of a "diencephalic discharge."

The physician did nothing but suggest an annual physical examination, for which she regularly returned. She had two uneventful pregnancies. At the age of 32 her previously labile blood pressure was found to be 160/100 mm. Hg or thereabouts, not returning to a normal diastolic with rest. As each year passed, a slightly upward trend was observed. At 40 it varied around 180/110 mm. Hg. Her mother died of a stroke of apoplexy at the age of 62, which upset her emotionally. She went to another physician, who found her blood pressure 200/116 and told her that she had high blood pressure. This was the first she knew of it and she became very agitated, saw her original physician in an excited state and he measured her blood pressure at 230/140 mm. Her fundi oculi showed spasm, but no other changes. He put her in hospital, upon which her pressure fell to 160/100 mm.; measured

concentration of circulating red blood cells and plasma proteins) diastolic hypertension is inevitable. Hypertension, then, can be considered a form of generalized vasospasm, a variant of normal *responses to circulatory stresses,* characterized by healthy blood and heart and by its chronic nature. Any one of several of the mechanisms which produce vasospasm can be involved in causing hypertension; new mechanisms can also arise at a time long after the organism would be dead or recovered from shock, had that been the initiating cause.

While we do not know the exact causes of generalized vasospasm, we do know a great deal about the mechanisms which produce it. The causes themselves lie in biochemical alterations in blood vessels, nervous tissue and organs of high metabolic activity. It is not enough to say that we do not know and therefore we must not try to know. For there are not many areas which have been so well studied, and there is little need to invoke *esoteric mechanisms to* the neglect of known ones. If one asked any physiologist what influences he would think could raise diastolic blood pressure, on the basis of experimental data he would choose autonomic nerves, kidneys and endocrine organs. He would not choose liver, thyroid, spleen or pancreas, however, but consider sympathetic nerves and their origins, renal blood flow and adrenal glands.

Clinical Chronic Hypertension: We can transfer these thoughts of our physiologist immediately to our own clinical experiences, viewing each case in their light. Let us take some typical ones.

1. A woman of 25 was found on routine examination to have a blood pressure of 152/88 mm. Hg. which after a rest fell to 138/82. Her mother had hypertension without sequelae. She had no symptoms, but her physician noticed that her heart rate was a little rapid and that she

at 56. At autopsy were found cerebral hemorrhage, massive; arteriosclerosis, moderate, of aorta, renal arteries, coronary arteries; marked, of circle of Willis, with rupture; arteriolar nephrosclerosis, moderate, cardiac hypertrophy (460 Gm.). Her adrenal glands were normal.

This sequence of events leading to early death can be reconstructed in the light of what is known. For many years this woman reacted to stressful situations by neurogenic vasospasm. Slowly the reversibility of this alteration became less and less, some gradually increasing factor being added which maintained a basal blood pressure at higher and higher levels, upon which was engrafted a widely fluctuating neurogenic component. This added factor was what killed her. Perhaps she would not have died so early, were it not for another disease, atherosclerosis, which began probably after her menopause and affected her cerebral arteries to such an extent that one ruptured under the high pressure.

2. A man of 25 was found to have a slightly elevated blood pressure and tachycardia when examined for the draft. His mother was hypertensive and his father had died of a coronary occlusion at the age of 51. Enuresis until the age of 8 had occurred, but he was free of further urinary symptoms and his urine showed no albumin. He went to his family doctor, who found a few bacteria in his urine with about 10 white blood cells per high power field in the centrifuged sediment, repeated cultures showed nonhemolytic streptococcus of the colon group in large numbers. He was given phenobarbital, and was accepted for duty in the Army. He had a creditable career and won several decorations for bravery. His discharge physical examination showed a blood pressure of 160/100 mm. Not until the age of 33 did he consult a physician for severe headaches and blurring of vision, which had appeared a month earlier. His blood pressure was 236/160

every 4 hours, it was normal during sleep (140/90) and dropped to 122/88 when tetra-ethyl ammonium chloride was injected intravenously. She was given phenobarbital, but was never the same. Investigative studies on the renal clearance of para-aminohippurate and inulin revealed reduction of renal plasma flow and relatively increased glomerular filtration rate, the profile of efferent arteriolar spasm.

Emotionally induced vasospasm had added to it another factor. In the first place, the neurogenic influence had increased. Secondly, the reversibility of the vasospasm had lessened.

She had her menopause at 45. By the age of 48, she was suffering from headaches every morning, anxiety, increased nervous tension and an inner sense of excitement. Her blood pressure was now constantly over 200 mm. systolic in spite of sedatives, but fell with rest to 160/110, fluctuating widely. During sleep induced by heavy sedation it did not fall to normal. Her fundi now showed some sclerotic, tortuous arteries; her electrocardiogram indicated enlargement of the left ventricle, seen also in x-ray photographs. Occasionally she had a trace of albumin in her urine, but she excreted 30 per cent of intravenously injected phenol red (PSP) in 15 minutes and her kidneys were able to concentrate urine to a specific gravity of 1.025. The blushing became more pronounced.

Now had appeared an irreversible component to the vasospasm, in that sleep did not completely abolish it. Signs of organic damage were developing. Rest, reassurance, sedatives, superficial psychotherapy and laying on of hands could not interrupt the vicious cycle.

She suffered her first stroke of apoplexy, a mild one, at 51, and recovered with little residual other than a limp. Hypertension persisted unabated and she died of another

kidney, and cardiac hypertrophy (520 Gm.) and dilatation His brain was edematous, his adrenals normal.

This man suffered from the "accelerated phase," or what is more exactly and descriptively called "malignant hypertension," and died young. He had the constitutional make-up of the hypertensive person, to which was added chronic low-grade smouldering pyelonephritis with an organism which does not produce pus but causes scar tissue. These two factors operating together shortened his life. By the time he died, there was little evidence left of the primary renal disease in the kidney distorted by nephrosclerosis.

3. An older man had a slightly elevated blood pressure at times of stress, which had been normal on regular examinations all of his life. At 49, however, he was refused life insurance because of a blood pressure of 170/110 mm. Hg. He had no symptoms except nervousness, but he was a tense, dynamic individual with excessive drive and ambition, somewhat of a perfectionist. Examination in hospital revealed no significant abnormalities except minimal left ventricular enlargement; studies on his renal plasma flow showed slight reduction with the calculated increased renal vascular resistance on the afferent side of the glomerulus. His blood pressure varied moderately but did not fall to normal levels during sleep or the injection of tetraethyl ammonium chloride. Renal "function" was normal. He was well, working hard and taking few vacations, until he was suddenly seized at age 54 with a severe retrosternal pain, and was admitted to hospital with an acute coronary occlusion. Other than minimal cardiac enlargement, a tortuous aorta and the usual signs of infarction there were no abnormalities. He recovered slowly but his blood pressure, normal or low during his illness, became elevated again to 180/110 mm. during rest and as high as 220/120 during activity. In spite of rearranging his life, he remained hypertensive until his second infarction, at 57, from which

mm., there was 3 plus proteinuria and microscopic hematuria, the ocular fundi showed early papilledema and soft "cotton wool" exudates but no hemorrhages, and his heart was slightly enlarged. He was able to concentrate urine to a specific gravity of only 1.019 and excrete only 15 per cent of the intravenously injected dose of phenol red in 15 minutes. Culture of the urine showed nonhemolytic staphylococcus, considered a contaminant, but intravenous pyelography revealed blunting of one upper calyx in the right kidney. His blood pressure altered little during deep sleep and when terta-ethyl ammonium ion was injected, his diastolic pressure fell from 158 to 145 mm. Hg.

This man, unlike his predecessor, had rapidly reached an "irreversible" stage of vasospasm. His blood pressure was "fixed" and his course was presumed to be rapidly progressive. Some organic renal component could be inferred from the earlier urinary findings and the pyelographic evidence, but this was asymptomatic. His family and early history suggested that he might be one of those persons who react to stress by vasospasm; added to this component was a chronically diseased kidney.

He refused admission to hospital, but was examined frequently during the next year and took the new Rauwolfia drugs continuously, without effect on his slowly rising blood pressure and deteriorating condition. Finally he was forced to seek help because of increasing dyspnea, but by that time the nonprotein nitrogen in his blood was 132 mg. per cent, his diastolic pressure 160 mm. Hg or more, he had suffered one attack of pulmonary edema and his ocular fundi showed many hemorrhages, hard exudates, soft exudates and papilledema. After a stormy downhill course he died of uremia complicated by congestive heart failure. At autopsy there was moderate generalized arteriosclerosis, advanced arteriolar nephrosclerosis with necrosis, a few depressed scars on the cortices of one

The curious thing about her obesity was its distribution over the trunk, upper arms and thighs. Her lower legs and arms were not obese at all. There was a "buffalo hump" and her face resembled those seen after overdoses of cortisone. Measurements of the sodium and chloride in her sweat showed values of 10 mEq./L. or less, levels found in Cushing's syndrome. She bruised easily and her ankles had a tendency to swell in the evenings She had a distinct mustache. Serum sodium was 145, chloride 101, CO_2 32.4 and potassium 2.8 mEq./L.

She did well, but remained hypertensive at home as it was impossible for her to restrict her salt intake and her appetite Not until she was 45 did her first episode of congestive heart failure bring her back into hospital. She died 2 years later, a cardiac cripple in the interim. At autopsy were found arteriolar nephrosclerosis, slight to none, moderate generalized arteriosclerosis, marked cardiac hypertrophy and dilatation (640 Gm.). There was a 1 x 1.2 cm. adenoma in the left adrenal cortex.

In her case, a functioning adenoma in her adrenal cortex was affecting both her salt and fat metabolism, the former influencing her hypertension. Better diagnostic methods would have allowed surgical removal.

These four cases are illustrative of distinct types of arterial hypertension encountered clinically. In actual practice one sees wide variations in their courses and sometimes bizarre mixtures. If the first patient had contracted glomerulonephritis in childhood or pyelonephritis during her pregnancy, or had by chance had a kink in her uteteropelvic junction due to an aberrant renal artery with stasis and infection, she probably would have exhibited more severe hypertension at an earlier age. If the second had not contracted pyelonephritis in childhood, he might have lived to become hypertensive in his 50's and died of heart failure or apoplexy in his 60's. If the renal arterial

he died. At autopsy there was found cardiac enlargement with focal myocardial fibrosis, a new infarct, arteriolar nephrosclerosis, *slight*, and generalized arteriosclerosis. Careful cross sectioning of the mouths of the renal arteries revealed some encroachment of their lumina by atherosclerotic plaques.

This man also probably had the constitution for hypertension. When he developed atherosclerosis, the slight narrowing of his renal arteries interfered enough with renal hemodynamics to cause a moderate hypertension. The elevated pressure worsened the atherosclerotic process, which in his case was lethal because it involved his coronary arteries. Hypertension itself did little direct, but much indirect harm, for he died before his time.

4. A woman of normal weight began to gain rapidly after her second pregnancy at age 22. Within 2 years her weight increased from 110 to 190 pounds, and slowly increased thereafter. At 35 she weighed 252 but on dietary *restriction lost 23 pounds.* Her menses had always been somewhat irregular and frequent, but in her 30's, periods [illegible]

[illegible]

[illegible]

(12 cm.) cuff, 186/122. Subsequently hypertension was moderate, blood pressure seldom exceeding 200/130 mm. and usually being about 200/120. Fundal changes were minimal. Studied in hospital, there was little evidence of vascular damage other than an enlarged heart. Periods of decreased urinary output followed by polyuria were noticed when her fluid balance was measured. Renal plasma flow and glomerular filtration rate were normal. Weight was lost very slowly on severe dietary restriction of calories, but restriction of salt promptly lowered blood pressure to normal levels. Her mother and one of three sisters were fat, hirsute and hypertensive.

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atheromata in the third had piled up enough to cause serious encroachment on the lumina, he might have entered the malignant stage, unless heart or brain gave out first. If the fourth had contracted pyelonephritis as well as her tumor, her course would have been shortened. Renal disease of any nature to interfere with blood flow, when combined with the "hypertensive diathesis," can increase the severity and shorten the course. The fact that hypertension is absent before azotemia in approximately 30 to 40 per cent of patients with renal diseases, points up the necessity for the presence of another factor to explain pathogenesis.

Pathologic Alterations: Dead house pathology does not always explain physiologic and biochemical alterations in disease. But it cannot be neglected. There are very few anatomic changes in hypertension, but they are characteristic.

1. Renal arteriolar and arteriosclerosis are almost universal in this disorder (2). Cases similar to our fourth are a notable exception (3, 4). The thickening, scarring and hyalinization of the afferent arterioles vary from slight to marked, with complete or almost complete occlusion of their lumina. Only in azotemia, and then only in half the cases, are the necrotizing arteriolar lesions seen (5, 6). These are called "malignant nephrosclerosis," a term which has little to do with non-azotemic "malignant hypertension." What has been little described are the earliest changes seen in hypertension, a thickening of the basement membrane of the glomerulus, later an increase in ground substance of the tuft, well followed in dogs (7) and observed in man. This change may be the result of increased intraglomerular pressure which must occur when efferent arterioles are constricted more than afferent ones.

2. Cardiac hypertrophy, and often dilatation, are almost

universal, although we have rarely seen normal sized hearts after sustained hypertension. This change is probably a work hypertrophy resulting from the increased cardiac work necessitated by the hypertension. It can be modified by associated atherosclerosis of the coronary arteries.

3. Generalized atherosclerosis is almost universal in this country, although cases without it are common in China (8).

Sequence of Development of Arteriolar Nephrosclerosis: This basic lesion, which by its very nature can cause renal ischemia and hypertension, is a result of hypertension. *In other words*, the altered hemodynamics of hypertension can lead to a pathologic change which further alters renal, and therefore peripheral hemodynamics. The evidence is clear on this point, in rats, rabbits, dogs and man (Chapter V). Therefore, at some point in two of our cases, renal vascular disease appeared after hypertension had become well established. Whether or not this secondary disease is responsible for the loss of reversibility of vasospasm is not known, but presumably it is not wholly accountable.

Comment: All biological phenomena can eventually be understood in terms of physics and chemistry. The remainder of this monograph is concerned largely with an examination of the biochemical alterations possibly operating to cause this disease, which is so eventually fatal as a rule, and which is so common to Western Civilization.

MECHANISMS OF SOME OF THE EFFECTS OF CHRONIC ARTERIAL HYPERTENSION

Degree of Peripheral Vasospasm in Chronic Hypertension: The vasospasm can be very intense in chronic arterial hypertension; in fact, it *must* be so in order to maintain the diastolic pressure at high levels. One can estimate the intensity of the vasospasm by measuring the pressure

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in an artery peripheral to complete intermittent mechanical occlusion (9-11). In man, only the brachial bed offers a convenient means of doing this. In Figure 1 are shown "asystolic arterial pressure gradients" in various types of hypertension. Persons with diastolic pressures from 100 to 200 mm. Hg have shown asystolic brachial pressures 18

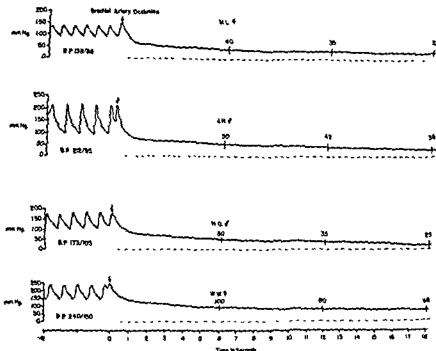


Fig. 1. Brachial asystolic arterial pressure gradient in man (9, 10). A needle connected to a recording manometer was inserted into the brachial artery and a sphygmomanometer cuff placed about the upper arm. After rapid occlusion of the cuff, the fall of pressure in the distal segment (the forearm) was measured. The level of pressure with no circulation is a measure of the degree of vasoconstriction opposing arterial run-off. Curves were obtained from a 46-year-old normotensive woman, a 54-year-old arteriosclerotic man without [illegible] hypertensive man [illegible] ralazine, and a 37- [illegible] ension. The curves are a function of diastolic pressure (11).

seconds after occlusion from 30 to 122 mm. Hg (average 65.8, normotension being 15 to 40, average 28.7 mm.), a finding surprising on the surface but expected when due consideration is given to hypertensive hemodynamics. The smooth muscle of all arteries and arterioles must therefore be in a state of chronic spasm, otherwise hyperemia would occur in those which are not.

Pathogenesis of Hemorrhagic and Exudative Retinitis: The lesions found in the fundi oculi when the diastolic pressure is high are those of edema, hemorrhage, deposits of proteinaceous or lipid material and scarring. Many ophthalmologists consider that hemorrhagic and exudative retinitis is due to localized ischemia of the retina secondary to excessive vasospasm. From a hemodynamic, anatomic and physiologic viewpoint this concept is hardly tenable, since: a) ischemia of a part does not usually cause edema without infarction; b) ischemia does not lead to hemorrhage, c) the retinal arteries and arterioles have rather thin muscular coats, and d) the lesions appear when the diastolic pressure is high, regress when it is lowered (sometimes to the point of producing retinal ischemia) and occur as a *manifestation of a sudden worsening* of the hypertension. A more logical explanation is that of plethora or excessive hyperemia. If the artery supplying an area of the retina were diseased so that it could not contract, and "healthy" vessels in the remainder of the body were made to constrict, hyperemia through that diseased vessel would result. Excessive flow and pressure would be transmitted to the capillary bed supplied by that artery. When venous outflow became insufficient to carry off the increased load, water, then plasma, and finally red blood cells would be forced through the capillary wall. This concept explains what we find: edema: "cotton wool" exudates, and hemorrhages. The "hard"

in an artery peripheral to complete intermittent mechanical occlusion (9-11). In man, only the brachial bed offers a convenient means of doing this. In Figure 1 are shown "asystolic arterial pressure gradients" in various types of hypertension. Persons with diastolic pressures from 100 to 200 mm. Hg have shown asystolic brachial pressures 18

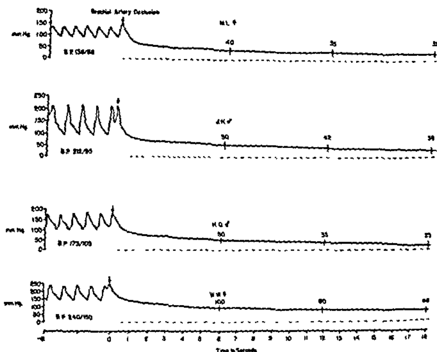


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Comment: The secondary effects of hypertension are relatively unimportant to this discussion, but they are of the utmost importance to the patient and to his therapy, for it is by them that hypertension becomes a fatal disease. A further, and often fatal, effect is discussed in Chapter VII.

exudates may be the scars of old hemorrhages and the protein and lipid remnants of exudation of plasma.

Since the arteries of the retina and brain are thin walled, weak structures compared to those in the remainder of the body, being in a media of higher external pressure, fairly generalized exudation and hemorrhage would be expected when systemic diastolic pressure rose to very high levels. It is probable that focal hemorrhages in the kidney, and perhaps in the gut, are the result of a high diastolic pressure through an artery or arteriole which is so diseased that it cannot constrict as much as the rest of the vascular bed. Therefore, many of the hemorrhagic and exudative lesions found in malignant hypertension are probably caused, not by excessive spasm proximal to the lesion, but lack of enough spasm to compensate for that of the rest of the vascular bed.

Pathogenesis of Necrotizing Arteriolar Lesions: In man, we find necrotizing lesions of the arteries and arterioles, usually of the kidney, only in nitrogen retention (5). Two influences are necessary, azotemia and a high diastolic pressure. Azotemia alone will not produce the lesions, for example, in uremia without much hypertension. On the other hand, hypertension alone will not usually cause the lesions in dogs (6) or in man. It is difficult to discover more than isolated cases in experimental animals without uremia (12). Both kidney (6) and a section of the small intestine can be protected from their occurrence by partial constriction of the main artery, even in severely uremic animals (13). Necrotizing fibrinous arterial degeneration, however, has been caused by the injection of organ, notably renal, extracts into nephrectomized dogs (14, 15). Therefore, both pressure and severe renal disease seem to be required for their occurrence.

This form of reacting to stress may be common to some human beings in many environments and of many races, although adequate studies have not been made. The old idea that a part of the population is "sympathotonic" and part "parasympathotonic" or "vagotonic" may have some basis of fact. Different species of animals show different types of reaction to stress; rats, cats, guinea pigs and rabbits not only exhibit opposite types but respond in aberrant ways to known pressor and depressor agents. There are at least two kinds of dogs, nervous overactive breeds which are hypertensive on the first and many subsequent examinations, and more or less phlegmatic breeds or crossbreeds which exhibit normal blood pressures and bradycardia (21). There is little reason to believe that the human organism differs radically in its fundamental reactions from those of higher animals.

Sympathotonic people are supposed to be subject to vasomotor phenomena, tachycardia and cardiovascular diseases, especially hypertension. Parasympathotonic people are supposed to be subject to bradycardia, a low blood pressure and gastrointestinal disorders, especially peptic ulcer. Another type of individual develops allergic reactions. In any population, all varieties and degrees of reactive ability can be expected, depending probably on the amount of imbalance between sympathetic and parasympathetic nervous function and the amount of external stress to which individuals are exposed. There may be several different constitutional types; we have not observed true extrinsic asthma in a hypertensive person and such allergic states as hay fever and urticaria are much less common than in the general population; duodenal ulcer is unusual in hypertension, although it exists (4); rheumatoid arthritis and most malignant tumors are seldom encountered in a hypertensive population (22).

Chapter II

BASIC OR CONSTITUTIONAL FACTORS

THE BASIC factors in arterial hypertension are those broad and ill-defined influences which cause a human being to become predisposed to the development of the disease. By arbitrarily separating basic traits from factors operating after the disease has become established, one can outline the areas of therapeutic approach and predict, with some success, efficacy of various forms of therapy.

Reaction to Stress by Vasospasm: The basic defect in persons predisposed to hypertension appears to be a reaction to stress by vasospasm or through vasomotor phenomena. Thus, Levy, Stroud, White and Hillman (15-18) found in Army Officers that transient hypertension, transient tachycardia and overweight each predisposed to the later development of hypertension, the last factor being the least significant. Long prior to these studies Hines found that when the stress of the first examination resulted in transient elevation of the systolic pressure to more than 140 mm. Hg, 63 per cent of the patients would develop hypertension 20 years later; if more than 150, 78 *per cent would exhibit it* (19). Critical predisposing diastolic levels were above 85 mm. Furthermore, Hines has shown that persons reacting by vasospasm to pain (cold pressor test) later usually develop hypertension (20). This manner of reacting therefore probably constitutes the underlying etiology, which lies in the constitution of the individual and is described but *not understood.*

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The ability, or habit, of reacting to stress by vasospasm, does not cause hypertension. It merely predisposes those individuals so constituted to the slow development of the disease. Other influences are probably operative which change reversible into irreversible vasospasm.

HEREDITY AND ENVIRONMENT

Heredity: The manner of reacting to stress by vasospasm is apparently an inherited characteristic. Hines has shown clearly that persons who so react have parents who are either hypertensive or react likewise to painful stimuli (23). The gross hereditary nature of chronic hypertension is well established, although Pickering disagrees with this idea (24); what makes up this predisposition has been little understood.

Thomas has clearly shown that cardiovascular disease is an inherited trait in the United States (25).

Personality: Patients suffering from chronic arterial hypertension in all stages of severity supposedly exhibit certain defects of personality, the qualities of which go to make mature and well-integrated individuals. The deficiencies have been considered as a subnormal level of assertiveness and tendencies towards obsessive-compulsive traits (26, 4). Anxiety, which may precede, or be a result of the illness, is also common (27). Whether these alterations are similar in the major psychosomatic disorders which result in irreversible organic changes (peptic ulcer, asthma) or are specific for one disorder, has not yet been clearly established. Likewise the effects of abnormal renal metabolites (primary amines and other substances) upon cerebral metabolism, which might enhance relatively minor functional derangements, are not known (Chapter III).

Environment: Without stimuli to cause a reaction, the reaction would not occur. The stresses, or stimuli, which

are a product of the environment and the attitude of the individual toward it, can be considered as initiating factors in the reaction. These influences vary widely from one person to another, involving the many faceted aspects of existence and adjustment to a prevailing social order. It is probable that the more complex society becomes, the greater are the environmental stresses consequent to adjustment to that society and therefore the stimuli to somatic reaction increase.

Pickering lately summed up his concepts on the relation of heredity, constitution and environment in hypertension (28): "To get these conclusions in perspective it may be said that, in its mode of inheritance, blood pressure resembles height, but that the size of the genetic factor is greater in the case of height. However, the regression coefficient certainly underestimates the size of the genetic factor, since we have been unable to allow for the day-to-day variability of blood pressure, and we have had to allow for the effects of age by a device which is probably valid when it is applied to large numbers, but not so accurate for individuals. By contrast, height shows quite insignificant variations from day to day and, for a considerable span of adult existence, is uninfluenced by age. The difference between the size of the genetic factor in blood pressure and height is probably *less than* regression coefficients suggest. Even so, it would seem justifiable to conclude that environmental factors are more important than hereditary factors in the pathogenesis of hypertension.

"These considerations lead to one further idea, which is so revolutionary that I merely lay it before you, knowing that your minds must instinctively reject it, namely, that the current concept of essential hypertension as a specific disease entity is largely an artefact. I venture to suggest that a restatement of the facts would define essen-

tial hypertensives as that group of the population with arterial pressures exceeding a certain value arbitrarily selected and in whom no specific cause can be detected to account for the high pressure. It is suggested that the factors causing it are factors operating generally on the population. Of these factors, the contributions of age, sex and inheritance can be defined approximately. The influence of environmental factors, which would seem by exclusion to be of great importance, remains to be explored."

We do not believe that this idea is so revolutionary, having entertained it for many years (29-31, 4). In Chapters V and VI will be discussed the factors operating generally on the population; in Chapter III this curious, ill-defined but well-known vasomotor manner of reacting which varies from individual to individual. These factors can now be examined separately.

CLINICAL IMPLICATIONS

Since persons predisposed to hypertension emotionally react to environmental stresses through somatic pathways by vasospasm, *in the very earliest stages* of the disorder some reversal of the somatic response can be expected if reversal of one or more of the psychic components could be accomplished. Many attempts to do so have been made. Psychotherapy has been extensively employed; in young individuals without organic disease it may teach the person either to avoid emotional stresses, to sidetrack the reactions thereto along other pathways or to resolve them without somatic reaction by means of logic and insight. In patients of older ages, with somewhat more advanced hypertension or with organic changes, however, little in the way of therapy can be expected. By analogy, while psychotherapy of peptic ulcer is useful to promote healing and to prevent further attacks, it is useless in relieving

pyloric obstruction with scarring secondary to repeated attacks. These defects of personality, however, are probably so deep-seated and fundamental to the growth of the individual that complete rebuilding becomes most difficult except in young people. In our experience psychotherapy has failed to modify the course of severe hypertension sufficiently to allow us even to suspect some beneficial somatic effect, and we have often watched patients deteriorate to eventual death in spite of the most vigorous forms available (an analyst reanalyzed by an analyst).

An environment considered unfavorable by the individual may be altered by moving to a new one; temporary effects upon the course of moderate and mild stages have been observed. The familiar fall in blood pressure when patients enter the hospital is an example. How permanent this change can be is not known. Minor adjustments in adverse environments, especially those caused by other individuals with whom the patient is in close contact, may for a time alter emotionally induced stresses (Figure 2).

Drugs, especially sedatives, have been employed for many years for the purpose of suppressing the emotional tension and lowering the threshold of reactions to stress. As a general rule, the more severe the hypertension, the less effective are sedative drugs and other such influences upon the disease. Contrariwise, the milder the hypertension, the more effective are measures aimed at the psyche and the emotional disturbance.

The effects upon the course of hypertension of any one or combinations of the above approaches is directly proportional to the relative influence of these factors in the total picture. Psychosomatic diseases may start as functional derangements mediated through autonomic nerves and end as organic conditions causing death. Therefore, while the beginning may lie in the psyche, as exemplified by the

word, constitution, that factor becomes increasingly less important as somatic changes occur. In reversible, early and very mild stages the disease may be controlled; as its somatic ravages progress less and less can be expected from attacks upon these etiological factors. Alterations of

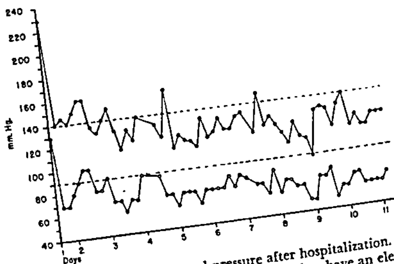


FIG. 2. Typical rapid fall of blood pressure after hospitalization. E. E. was a 39-year-old woman who was first discovered to have an elevated blood pressure six years previously at the time of pregnancy complicated by pyelonephritis. During the intervening years her blood pressure was always elevated in a physician's office. Six months and one month prior to admission she suffered two attacks of severe headaches, numbness and weakness of one side of her body, and loss of consciousness for one to three hours, with gradual recovery during the following week. Her blood pressure was said to have varied between 230/130 and 210/110 mm Hg for 2 years She complained of dyspnea on exertion and dizziness. On examination there was one small retinal hemorrhage Blood pressure was 238/136. Her heart was enlarged to the left in x-ray photographs. Renal function was excellent. No cause for the attacks was discovered on careful neurologic examination. The first pressure shown (230/130 mm. Hg) was measured by both the intern and assistant resident the night of admission; subsequent ones were measured by nurses beginning the following morning. (From, Schroeder, H. A., and Perry, H. M., Jr.: *Am. Heart J.*, 51:776, 1956.)

disturbed emotional and nervous functions cannot be expected to dissolve scar tissue.

Although Bays and Scrimshaw disagree (32), from all the evidence available we can be fairly certain that hypertension not secondary to renal disease is a disorder fairly well confined to persons exposed to the influences of Western Civilization (4). For example, it is unusual in parts of Africa (33) and China (8), very prevalent in American Negroes, but rare in American Indians in the Southwest (34). In Uganda, only 2 6 per cent of autopsied cases of heart failure were due to essential hypertension: the same percentage to atheromatosis and none to coronary thrombosis; renal hypertension, however, accounted for 16 per cent (35). Surely one is led to conclude that environmental influences are of the greatest importance, for *in this* country probably half the cases of heart failure are hypertensive in origin. When viewed from this outlook, many discrepancies in the geographic incidence of hypertension fall into line.

Comment: There are three apparent facts upon which one can speculate.

1. The predisposition to hypertension is inherited.
2. There is an emotional overlay in the disease which may be either primary or secondary.
3. The disease is confined more or less to civilized or partly civilized people, without any particular ethnic, cultural or social pattern, suggesting that environmental factors such as food habits or contact with industrialized society plays an initiating role.

Chapter III

NEUROGENIC EFFECTOR MECHANISMS

INTRODUCTION

WHILE yet unproven, it seems clear that the sympathetic nervous system is somehow relatively or absolutely overactive in prehypertensive and hypertensive states, especially when there is no demonstrable organic renal component. The indirect evidence, suggesting rapid alterations in the nervous control of blood vessels, is as follows:

1. The blood pressure is labile and widely variable (Fig. 3).
2. Traube-Hering and respiratory variations in blood pressure are often marked (36, 37) (Fig. 4).
3. The vasospastic response to painful stimuli and to emotion is often exaggerated (20, 38-41).
4. The pressor effects of central vasomotor stimuli, such as inhalation of carbon dioxide and holding the breath, is often increased (42-44).
5. Blocking sympathetic nerves by drugs or surgery abolishes many of these exaggerated vasospastic responses to pain and emotion (45, 46).
6. Drugs acting partly on the central nervous system lower the blood pressure more or less *(vide infra).*
7. Sustained hypertension can be produced in certain animals by interfering with sympathetic and cerebral nervous mechanisms (47-50).

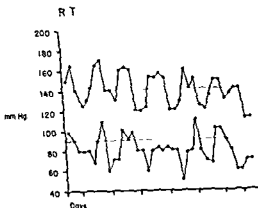


Fig 3 Daily and nightly fluctuations of supine blood pressure in an 18-year-old man in the "pre-hypertensive" phase. His kidneys and heart were normal by all tests Note that the rise in pressure occurs only during the day The divisions between each 24 hour period are at midnight

The evidence against neurogenic effector mechanisms operating in sustained human "neurogenic" hypertension is poor and usually explicable by an analysis of the cases employed for experimentation or by an understanding of the processes concerned in neurogenic vasoconstriction. At present, no one doubts the existence of neurogenically induced vasospasm in man. We must emphasize, however, that in chronic human arterial hypertension the relative parts played by neurogenic and other mechanisms vary considerably from patient to patient (Chapter IV) The contrary evidence follows:

1 Little or no increase in urinary catechol amines is usually found (51) Norepinephrine, however, is liberated at nerve endings and metabolized or conjugated *in situ* before its products reach the blood stream. Therefore overproduction must be great enough to saturate oxidative and conjugative enzymes in order to allow enough to spill

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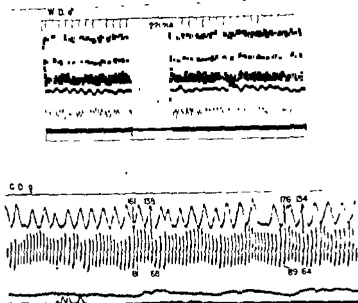
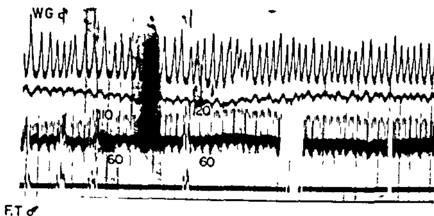


Fig 4 Spontaneous variations in blood pressure measured photokymographically by direct arterial puncture W G normal and normotensive, variation 9 6 mm Hg F, T normotensive convalescent from severe acute poliomyelitis with probable slight involvement of the hypothalamus or medulla giving rise to neurogenic vasomotor instability, variation 41/20 mm Hg W D fairly severe nephrogenic hypertension, variation 13/13 mm Hg I H severe neurogenic hypertension, variation 35/25 mm. Hg W D (repeat after several days rest) variation 7/3 mm Hg C O mild neurogenic hypertension variation 42/25 mm Hg By indirect measurement C O's systolic pressure, when taken by a white coated physician, varied from 180 to 240 mm and her diastolic from 150 to 100 mm, nurses always obtained readings 20 to 30 mm. lower The wide, fairly regular tracings are those of respiration, the smaller ones of a plethysmograph on the finger Camera speeds 1 25, 5 and 25 mm per second



F.T ♂

155
121
156
115
105
75
100
75

WD ♂
232
219
225
212
135
117
125
110

1H.8
248
215
250
220
145
30
155
130

Several influences arising in the brain can cause experimental hypertension, such as noise (54), internal hydrocephalus (46), puncture of the third ventricle (55), tying off the arterial supply (49), all of which may interfere with blood flow or nervous function in a regulatory area. Similarly, in man increased intracranial pressure, certain brain lesions of viral, vascular or traumatic origin (fractures of the base of the skull, encephalitis, poliomyelitis), certain tumors, and hypothalamic injury can lead to chronic neurogenic hypertension or its acute equivalent (56).

There are four possibilities to explain the cerebral role in human hypertension: 1. The nervous temperament of the hypertensive person, with the frequent finding of anxiety and frustration, may initiate repetitive discharges through the sympathetic nervous system. Subnormal assertiveness, obsessive-compulsive traits and anxiety are said to be common to the "hypertensive personality" (26, 27). This hypothesis has always been an attractive one, but is unproven and most difficult to investigate with the tools at hand.

2. The peripheral metabolic abnormalities associated with hypertension may cause stimulation of cerebral metabolism. It is known that many primary amines cause central excitatory effects. Amphetamine (Benzedrine) is a good example. In fact, Mann and Quastel (57) suggested that the central stimulant action of *dl*-phenylisopropylamine (Amphetamine) is related to its inhibition of tyramine oxidation by amine oxidase in brain. On this basis, Fellows and Bernheim (58) examined a large number of structurally related salts in rats and found in many instances good correlations between central stimulation and cerebral amine oxidase inhibition. Clinically, the excitatory actions of epinephrine and a number of derivatives are well known; we have observed profound and

over into blood and be excreted in urine. Actually some patients do have moderately increased amounts in their urines (51b), about a third.

2. No increase in circulating catechol amines can be detected (38).

3. Many patients do not show all of the typical exaggerated pressor responses nor the marked depression of blood pressure induced by drugs or surgery (52). The logical explanation is that another vasospastic process is largely operative in such individuals.

"Although neurogenic pathways effecting vasoconstriction are intimately connected, it is necessary to examine each component of the sympathetic nervous system in the light of its role and of specific effector substances and chemotherapeutic agents. Some of these are known; some must be postulated The brain and its appendages exert a profound effect upon normal vasomotor tone and are probably involved in many forms of generalized vasospasm."As Starling said (53): "No pathology will be adequate which does not take into account the sensitiveness of the vasomotor centers to the changes in the circulation." Considerable information on pathogenetic factors can be learned from the actions of specific drugs; more, perhaps, than by direct experiments

CEREBRAL MECHANISMS

The areas within the brain initiating or transmitting sympathetic discharges or regulating vasomotor tone are three: the cortex, the hypothalamus, and the vasomotor center. Just how these areas are involved in the hypertensive process is not known What is known, however, is that certain drugs modify their activities and partly affect the amount of peripheral vasospasm neurogenically induced.

the hypothalmus or vasomotor center may initiate somatic sustained neurogenic pressor responses. While such lesions have been found in some cases (64) and may account for the hypertension of some older persons, there is no uniform correlation with all cases and this idea remains merely an attractive hypothesis.

SPECIFIC DRUGS

Whatever the cause of the increased nervous excitability of hypertensive patients, many agents have been used to counteract it and thus produce variable effects upon blood pressure, depending upon a) the relative part played by the brain, b) the effectiveness of the drug, and c) the ability of the patient to tolerate side effects. Sedatives have been used for many years in an attempt to allay tension and anxiety. They will not be discussed, since their employment is wide.

Serotonin Antagonists: Reserpine causes depletion of cerebral serotonin in the experimental animal (65, 66); platelet serotonin is also reduced to a low level. The net effect of this agent, a chemical analogue of yohimbine, is to produce on affect the equivalent of a prefrontal lobotomy (67). Its locus of action appears to be pre-hypothalamic and subcortical; the posterior hypothalamus, wherein lie the sympathetic centers, is partially blocked (68). The effect of the drug is cumulative, requiring a week or two for oral doses to act maximally; although rapidly excreted, the drug itself leaves "serotonin acceptors" in the brain blocked for long periods. Aside from its "tranquilizing" action, [illegible] thetic c[illegible] acidity [illegible] has appeared *de novo* or become activated; in one of our cases chronic ulcerative colitis has developed (69). Various cerebral symptoms are

uncontrollable anxiety induced by intravenous isoamylamine in laboratory workers, for example. Therefore, some circulating primary amines may induce cerebral stimulation. Fast diffuse dysrhythmias in the electroencephalograms are common in human neurogenic hypertension (4); this picture can be produced by certain amines (59). Thus, a vicious circle could be established, from periphery to brain to periphery, the initiating organ not being known.

Serotonin, a derivative of tryptophane, has received the greatest interest in this regard, since its isolation from platelets. This primary amine occurs in brain and may have a definite function in nervous tissue (60), as may other similar substances. It is interesting, and perhaps more than coincidental, that malignant carcinoid of the appendix, a serotonin-producing tumor, apparently causes a peculiar flushing phenomenon which is similar to the "diencephalic blush" which we associate with neurogenic hypertension (61, 62). Injection of serotonin in man causes a variety of subjective symptoms not apparently associated with anxiety, but similar in some respects to those seen following other substituted primary amines (63). The role of several tertiary and quaternary nitrogenous compounds on nerve conduction and synaptic transmission is barely beginning to be appreciated.

3. There is either excessive production of stimulating substances *in situ* or generalized inhibition of those enzymes concerned with metabolizing such substances. For example, if every sympathetic nerve ending contained a molecule inhibitory to amine oxidase or to the enzyme conjugating norepinephrine, the normal "tone" of sympathetic nerves would be enhanced. There are no proofs of this theory.

4. Local vascular lesions of an arteriosclerotic nature in

TABLE I—(*continued*)

	Reserpine (*123 subjects*)	*Chlorpromazine* (*137 subjects*)
Epistaxis	2.4	0
Blurred Vision	0	1.5
Dry Mouth	0	1.5
Heart Burn	0	1.5
Edema	7.3	5.1
Pruritus	1.6	1.5
Dermatitis	0	9.5
Jaundice	0	5.1
Hepatomegaly	0	2.2

also induced, among them vivid dreams and nightmares. One of the most interesting of its actions is to cause, in a sizeable percentage of people, nervousness, insomnia, agitated depressions and suicidal tendencies (70); used to treat these symptoms in psychotic individuals, it can backfire and produce them. Truly, this most interesting drug has begun to open up a wide field in our understanding of mental illness

[illegible]

well and hypothalamic action has been postulated (74). While it can cause some depression of the sympathetic nervous system, it can also produce symptoms of stimulation in some individuals (Table I) with hypertension and tachycardia. Likewise, its antiemetic action may be reversed in other subjects.

Other antimetabolites to serotonin are not used in hypertension; yohimbine, because of its nephrotoxicity, and d-lysergic acid diethylamide, which produces schizophrenic-like states (63, 66). The most interesting are the nitroindoles, which are true competitive antagonists, blocking

TABLE I

RESERPINE AND CHLORPROMAZINE

INCIDENCE OF SIDE REACTIONS AND TOXIC EFFECTS IN NORMOTENSIVE PATIENTS

	Reserpine (*123 subjects*)	*Chlorpromazine* (*137 subjects*)
Sympathetic N. S. Inhibition	31.6	14.6
Hypotension	17.0	3.7
Bradycardia	1.6	0
Diaphoresis	3.3	0
Chilliness	5.7	7.3
Nausea	2.4	5.1
Vomiting	7.3	0.7
Diarrhea	0*	0.7
Exacerbation of Peptic Ulcer		
Sympathetic N. S. Stimulation	0	6.6
Hypertension	0	8.8
Tachycardia	0	3.7
Hyperthermia		
Cerebral Symptoms		
Excessive Flushing	9 0	0
Dizziness	5.7	5.1
Fatigue, weakness	9.7	2 2
Syncope	1.6	0 7
Excessive Drowsiness	17 8	12 4
Tremulousness	15.4	0.7
Myalgia	3.3	0
Ataxia	5 7	0
Parkinsonism	1 6	0 7
Vivid Dreams	2.4†	2.2
Agitated Depressive Psychosis	±5‡	
Other		
Nasal Stuffiness	27 6	1.5

* We have seen 4 cases.

† Higher in our experience.

‡ Author's series.

(From Zeller, W. W., Graffagnino, P. N., Cullen, C F., and Reitman, H. J.: Use of chlorpromazine and reserpine in the treatment of emotional disorders. *J A. M. A*, *160*:179, 1956.)

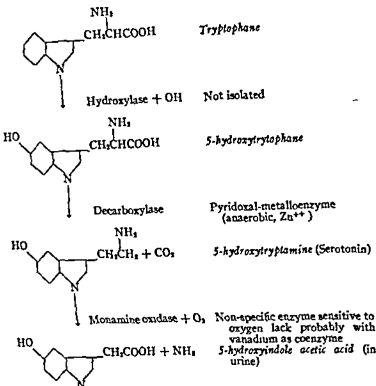


FIG 5 Metabolism of serotonin, modified from Sjoerdsma *et al.* (61).

phane and its decarboxylation (Fig. 5). The hydroxylase has not been discovered, but the renal decarboxylase (71) contains a pyridoxal-metal complex as a coenzyme (72), like many other amino acid decarboxylases. Serotonin is metabolized by monamine oxidase (Chapter IV), an enzyme requiring oxygen and sensitive to oxygen tension. Therefore, renal ischemia could allow the formation of serotonin by anaerobic decarboxylation, but prevent deamination *in situ* due to oxygen lack. Serotonin would then escape into the blood and be deaminated either in the lungs or on arterial smooth muscle. While it is doubt-

the action of serotonin on smooth muscle; they have not been employed more than sporadically with little effects.

A newer sedative, 2-methyl-2-n-propyl-1,3-propanediol dicarbamate (meprobamate) apparently selectively blocks interneurons primarily on the thalamus and caudate nucleus (75). There is little or no effect upon the autonomic nervous system. This drug should therefore prove a tool for controlling anxiety in mildly hypertensive patients and thus estimating the role which nervous tension *per se* plays in minor elevations of blood pressure.

Comment: None of these agents are more than mild antihypertensive drugs. One or another may control moderate or intermittent elevations of blood pressure, especially when associated with emotional tension, but they are relatively valueless, except as adjuncts, in more severe cases. Obviously the sustaining mechanism for severe hypertension lies elsewhere than in the brain, although initiating mechanisms may be there; in cerebral edema, however, a large neurogenic influence may be exerted. The most potent and specifically acting drug can do no more than inhibit the relatively minor role which the brain contributes to the process of generalized vasospasm. Even after destruction of much of the brain by atherosclerotic disease, to the point of causing a vegetative existence, established hypertension may not disappear.

Serotonin is one of the newest agents discovered to be involved in cerebral interneurone transmission. Of great interest is the fact that this primary amine apparently has a specific affinity for cortical pathways to the posterior and lateral hypothalamus. (Too much could stimulate and cause emotional tension, a normal amount interest, initiative and drive, while too little could result in mental depression) Serotonin is found in quite primitive marine organisms; it is formed by the hydroxylation of trypto-

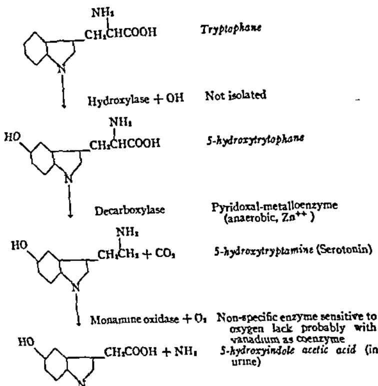


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ful that serotonin is concerned directly in hypertension, injections into hypertensive, but not normotensive, animals and man are moderately pressor, and this interesting substance in slightly increased amounts could represent an abnormal metabolite causing some symptoms and a small portion of the vasospasm.

CAROTID SINUS MECHANISMS

There is no good evidence that the carotid sinus mechanism is underactive in the usual case of hypertension. Chronic sustained hypertension can be produced in dogs, *however*, by ablation of the carotid sinus and *aortic* depressor nerves (76); while this state is true "neurogenic" hypertension, after several years the renal lesions of arteriolar nephrosclerosis develop (7). In our experience, this form of hypertension is not dependant solely upon increased cardiac output as there is intense peripheral vasoconstriction under anaesthesia (10). A clinical counterpart may be suspected in patients with atherosclerotic narrowing of the mouths of the innominate and left common carotid arteries. That an appreciable degree of narrowing is uncommon may be suspected from the clinical observaitons that symptoms of severe cerebral ischemia do not usually follow reduction of elevated blood pressure to normal; that some degree of obstruction may occasionally be found is suggested by the vague discomfort accompanying normotension seen in many atherosclerotic hypertensive individuals. (While hardening of the carotid sinus wall and local atherosclerotic narrowing have been suggested (77), these lesions are unproven as causes of chronic hypertension.)

Specific Drugs: There is a group of drugs from plants of the veratrum family which do affect the carotid sinus, sensitizing the pressor receptors and thus increasing the activity of the depressor mechanism (78). Protoveratrine

A and B are the most purified alkaloids, usually found in a mixture and most difficult to separate. They cause depression of blood pressure and bradycardia; nausea and vomiting may result from vagal stimulation (79). The pathway is through the glossopharyngeal nerve to the vasomotor center (78). When doses are adjusted properly, intermittent normotension can result from the careful use of protoveratrine and its impure derivatives (80). Apparently tolerance is quick to appear and disappear, so that sustained normotension will not result unless adjuncts operating on other mechanisms are used. Whether or not this drug is a true antihypertensive agent affecting the basic process, is unclear, although the hemodynamic response is quite favorable (Table II).

Baroceptor Changes: McCubbin, Green and Page (81) have recently shown that the carotid sinus and aortic depressor mechanisms are "set" at a higher level of pressure in renal hypertensive dogs than in normotensive dogs. They propose the ingenious theory that this higher "setting" maintains the hypertension even when the initiating mechanism (renal ischemia, pheochromocytoma, toxemia of pregnancy) is removed. Thus renal hypertension slowly becomes neurogenic buffer nerve hypertension, as Ogden has suspected in rats (82). If this were so in man, one would expect that late chronic hypertension would respond to the use of drugs or surgery acting on nerves better than would early hypertension. Clinically, the opposite holds true; therefore, this attractive hypothesis necessarily can be discarded as applying to most human cases.

SYMPATHETIC NERVOUS MECHANISMS THROUGH GANGLIA

All autonomic nerves after emergence from the spinal cord pass through ganglia. In general, sympathetic nerves form synapses in paravertebral ganglia, while parasympa-

TABLE II

CARDIOVASCULAR EFFECTS OF PROTOVERATRINE AND GANGLIONIC BLOCKING AGENTS IN MAN

	Normal		*Hypertensive*	
	Epinephrine	*Norepinephrine*	*Protoveratrine*	*Ganglionic Blockade*
Cardiac				
Heart Rate	+	−	−	−
Stroke Volume	+	+	+	−
Cardiac Output	+	0	0	−
Coronary Blood Flow	+	+	?	?
Blood Pressure				
Systolic Arterial	+	+	−	−
Mean Arterial	+	+	−	−
Diastolic Arterial	−	+	−	−
Mean Pulmonary	+	+	?	−
Peripheral Circulation				
Total Peripheral Resistance	−	+	−	−
Cerebral Blood Flow	+	0−	0	0
Muscle Blood Flow	+	0−	+	+
Cutaneous Blood Flow	−	+	?	+
Renal Blood Flow	−	−	0	−*
Splanchnic Blood Flow	+	0	?	−

* Transient.

thetic nerves end in ganglia at more peripheral (organ) areas. The adrenal medulla receives preganglionic fibres which cause discharges of epinephrine, a sympathetic effector substance, into the circulation; therefore it may be considered a "ganglion" in the broadest sense of the term.

The chemical mediator of ganglionic transmission is a quaternary ammonium compound, acetyl choline. Whether or not other compounds containing tetracovalent nitrogen

or choline esters can act as transmitters is not known. Acetyl choline (or its derivatives) apparently is essential for synaptic transmission in all ganglia, both sympathetic and parasympathetic. Nicotine in small doses is a stimulant.

The ganglion itself governs the integrity of the postganglionic fibres, much as the spinal nuclei control the integrity of their neurons. Removal of a ganglion is probably followed by degeneration of the nerve; after a few days sensitivity of the nerve ending to circulating vasoconstrictor substances develops. Therefore, in order to perform an adequate sympathectomy, preganglionic fibres must be cut.

Specific Drugs: Chemical ganglionic blocking agents usually contain quaternary ammonium, stabilized tetracovalent nitrogen competing with acetyl choline or other more labile nitrogenous substances. Numbers of such compounds exist. The simplest one of the group is tetraethyl ammonium ion, known for many years as a vasodilating drug of short action. Longer action is achieved by lengthening the carbon chain and doubling the nitrogen group (pentamethonium, pendiomide, hexamethonium), or by adding cumbersome ring structures (pentolinium, chlorisondamine). All act in a similar manner, differing only in duration of action and degree of gastrointestinal absorption. A new blocking agent, mecamylamine (Inversine), differs considerably in structure, being a complex spatial molecule with trivalent nitrogen as a secondary amine. It has the advantage of virtually complete absorption from the gastrointestinal tract (83). Comparative doses are shown in Table III (Fig. 6).

Since acetyl choline also mediates nerve transmission to striated muscle, it may appear strange that curariform

paralysis does not result from ganglionic blocking agents. Some anatomical or chemical differences between ganglia and motor end plates undoubtedly exist, for hexame-

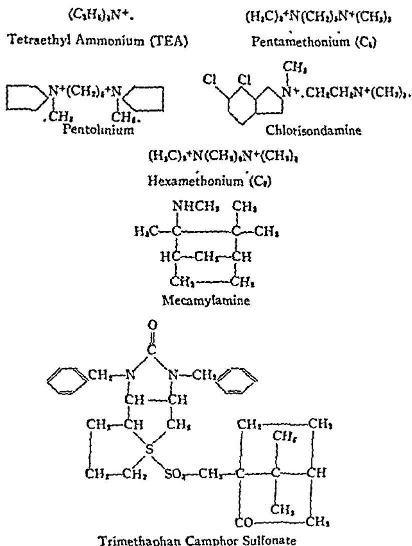


FIG. 6. Structural formulae of ions of some ganglionic blocking agents. The salts are not shown. The last, known as Arfonad, is *only used intravenously*. Note the quaternary or tetracovalent nitrogen groups which are the active ones, and the camphane structure of those with trivalent nitrogen.

TABLE III

COMPARATIVE DOSES OF GANGLIONIC BLOCKING AGENTS* (SEVERE ADULT HYPERTENSION)

Ion	*Usual Effective Oral Dose*		*Maximum Tolerated Oral Dose*		*Duration of Action of Oral Drug*	*Usual Effective Parenteral Dose‡*
	Single Dose mg	*Daily Dose mg*	*Single Dose mg*	*Daily Dose mg.*	*hrs.*	*Single Dose mg.*
Tetraethyl Ammonium	†	†	†	†	½–1	500
Pentamethonium	500	2500	?	?	3	25
Hexamethonium	500	2500	1000	6000	4	25
Pentolinium (Ansolysen)	100	500	800	4000	4–5	25
Chlorisondamine (Ecolid)	50	250	200	1000	4–6	15
Mecamylamine (Inversine)	10	50	25	150	4–8	10

* When combined with hydralazine.

† Sublingual doses effective, oral not.

‡ *Initial* dose much smaller. Wide variation as tolerance develops.

thonium ion in large doses can exhibit curare-like actions. Lengthening of the carbon chain to 10 atoms results in a curariform drug, decamethonium; curare itself contains tetracovalent nitrogen, and succinyl choline has a similar action (84). The longer the chain from 5 to 10 carbon atoms, the greater is the paralytic effect.

The cardiovascular *effects of ganglionic blockade* are summarized in Table II. Thus, ganglionic blockade, while lowering blood pressure, does not act primarily upon all of the functions disturbed in hypertension. Furthermore, sympathetic nervous inhibition at the ganglionic level is also associated with parasympathetic nervous inhibition. Renal and splanchnic blood flow are altered in the wrong direction. Continuation of these disturbances could cause serious consequences, were it not for some unknown readjustments which take place within the organism, counteracting the changes. While the effects of these agents in opposing the hypertensive process are real and offer evidence for the role of the sympathetic nervous system in pathogenesis, they are not all to be desired. Presumably they differ from the effects of surgical sympathectomy. The subject of the specificity of these drugs on the basic processes concerned in vasospasm is open and arguments pro and con the question of whether or not the observed effects are truly antihypertensive have validity on both sides.

SYMPATHETIC NERVE ENDINGS

The chemical effector substance of the sympathetic nerves is norepinephrine. On stimulation of a nerve, this primary amine is released at the junction of nerve and organ or smooth muscle fibre. Infusion of norepinephrine intravenously mimics the cardiovascular profile seen in sustained arterial hypertension (Table II), and a similar

"picture is caused by norepinephrine-secreting pheochromocytomata. Therefore, the neurogenic component of hypertension can be considered to be mediated by this substance."

Norepinephrine is derived either from dihydroxyphenyl serine, by decarboxylation, or from tyramine, by hydroxylation of the benzene ring and the β-carbon. The first appears the most facile method for the nerve ending to make this substance rapidly. It is inactivated *either through* conjugation, through oxidation of the amine nitrogen by monamine oxidase, or by rearrangement of its molecule *to form an indole nucleus* through oxidation by polyphenol oxidase, a copper enzyme.

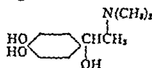
The ideal agent for counteracting norepinephrine has not been found There are a number of sympatholytic drugs which inhibit its action on nerve endings and which are effective for short or longer periods in experimental animals. We list them only as directions for research. These may be grouped roughly as derivatives of benzylamine, of phenethylamine, of ergot, of benzodioxane, and of imidazole (Table IV, see page 48). All contain tertiary substituted nitrogen.

Derivatives of Benzylamine: Dibenamine, a complex structure remotely related to norepinephrine, forms tight bonds at sympathetic *nerve endings*, preventing the action of this constrictor substance, probably by competitive inhibition. The action is prolonged for *many* hours. It is *moderately* effective by mouth, much more so intra*venously*. There are many side effects in man, especially on the brain. Dibenamine and its relatives are the most effective sympatholytic agents known at present, but their value in hypertension *remains to be* proven.

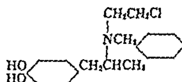
Derivatives of Phenethylamine: We had an opportunity of testing a group of primary amines in rats for sympath-

olytic qualities, some of which were given intravenously in man.

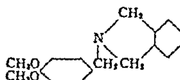
Those blocking norepinephrine in the rat had the following formulae:



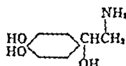
SKF-1298-A



SKF-669-C

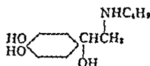


Mer-11

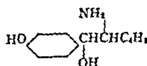


Norepinephrine

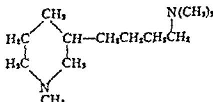
The nitrogen in these compounds was completely substituted, all being tertiary amines. There was, however, no consistency in the results, for the following gave no blocking action:

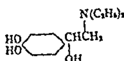


SKF-690-A

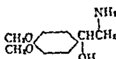


SKF-1222

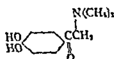




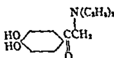
SKF-1297-A



SKF-1277-A



SKF-1299-A



SKF-1300-A

Renal hypertensive dogs responded by a lower diastolic pressure only when SKF-1298-A was given.* SKF-690-A was a powerful epinephrine-like substance in man, causing vasodilatation and an increased cardiac output with fall in diastolic pressure. SKF-1298-A caused symptoms suggestive of cholinergic stimulation; two others were without effect.

The experiments of Furchgott are of interest. Using the spirally cut rabbit's aorta as a source of smooth muscle, he was able to show on this simple system how certain agents, such as dibenamine, block all constrictor amines, others block some and others block only a few (85). Therefore, it is likely that very specific agents can be found which will pick out one primary amine, and not others, for inhibition

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* None of these substances specifically depressed elevated blood pressure in the anaesthetized renal hypertensive rat without affecting normotensive rats.

TABLE IV

ACTIONS OF ADRENERGIC BLOCKING AGENTS IN MAN*

Function	*Dibenzyline*	*Dihydrogenated Ergot Alkaloids*	*Phentolamine and Tolazoline*	*Benzodioxanes*
Principal Action on Epi- or Norepinephrine	Both	Epinephrine	Both	Epinephrine
Cardiovascular				
Cardiac Output	Unchanged	Unchanged or Decreased	Unchanged	Decreased?
Blood Flow—Femoral	Increased	Increased	Increased	Unchanged
—Mesenteric	Unchanged	Decreased		?
—Renal	Unchanged	Decreased	Decreased transiently	?
—Cerebral	Unchanged	Unchanged	Decreased	
Coronary arteries	Dilated ?	Constricted	Dilated	Constricted
Peripheral Resistance	Decreased	Decreased	Decreased ?	Variable
Principal Adverse Effects				
Central Nervous Stimulant	+	+	0	+
Tachycardia	+	+	+	+
Tissue injury, local	+	0	0	0
Nausea and Vomiting	+	+	0	0
Duration of Action	Days	Hours	Minutes	Minutes

* After Goodman and Gilman (84).

Derivatives of Ergot: The dihydrogenated ergot alkaloids have the ability of blocking adrenergic impulses, but their action is greater on epinephrine than on norepinephrine. Toxic effects limit the tolerable dose so that useful blockade is rarely produced. They must be given sublingually or parenterally; their effects in hypertension vary but are usually inconsistent.

Derivatives of Imidazole: Tolazoline (Priscoline) and Phentolamine (Regitine) are two short acting moderately effective adrenergic blocking agents containing both benzene and imidazole rings. Phentolamine, while opposing the actions of both epinephrine and norepinephrine, is useful for the most part only as a test substance for circulating catechol amines. It usually causes a transient fall of blood pressure in hypertensive patients, suggesting that some sympathetic tone is present; in azotemia the effect may be prolonged and profound. Cardiac stimulation is the rule. Tolazoline is readily absorbed and excreted unchanged in the urine; phentolamine is apparently metabolized up to 90 per cent of the dose. The short durations of action limit their use.

The Benzodioxanes: Piperoxan (Benodaine) and *prosympal*, first synthesized by Fourneau, act transiently, usually by vasoconstriction. They do oppose, however, the action of epinephrine, probably by competitive inhibition; norepinephrine is blocked only by toxic doses. Side effects are many, especially smooth muscle stimulation, and limit their use except in epinephrine-producing pheochromocytomas.

Comment. All of the known adrenergic blocking agents fail to block cardiac accelerator mechanisms: tachycardia and increa[illegible]
clinical u[illegible]

vasoconstrictor amines is greater than is the blockade of nerve impulses; dibenamine has less differential activity in this respect. The ideal agent for chemical sympathectomy is one which prolongedly blocks norepinephrine at all vascular nervous endings, including especially those in the heart. This agent has not been found; if it can be, it should prove the best agent for controlling the neurogenic factor in human hypertension.

Other Effector Substances: While the role of other "sympathomimetic" amines in hypertension is not established, they are probably present in excessive amounts and may contribute to symptoms if not to vasospasm. Decarboxylation of amino acids by kidney is an anaerobic process (86, 87) while deamination is an aerobic one (88), the enzymes, monamine oxidase and possibly diamine oxidase being sensitive to oxygen lack (89). Under these conditions any amino acid decarboxylated by the kidney could form amines by partial interrupted metabolism, altering the locus of deamination from kidney to peripheral smooth muscle or liver. The level of primary amines in hypertensive blood is usually high (4, 90, 91). This error of metabolism will be discussed at length in Chapter IV.

CLINICAL IMPLICATIONS

In the absence of a good specific adrenergic blocking agent which also blocks the cardiac sympathetics, we are forced to use combinations of drugs, depend upon ganglionic blockade, or affect the carotid sinus mechanism. Combinations of adrenergic blocking agents, such as dibenamine derivatives and protoveratrine, have been advocated, the former to block nerve endings and the latter to slow the heart. In fact, one such preparation also contains reserpine, which tends to cause bradycardia. Such

"pousse café" combinations are to be avoided; all drugs give reactions and side effects, and it would be difficult to assess the vomiting induced by dibenamine and that by protoveratrine in such a mixture.

The "toxic" or side reactions of reserpine and chlorpromazine have been given in Table I. The most serious late toxic reactions of reserpine are those of agitated depressive psychosis, which are often accompanied by suicidal tendencies and may lead therefore to death. Of chlorpromazine, there are hepatic disease and granulocytopenia; some 17 deaths have resulted (92). Chronic administration of any drug given to control, not cure, a chronic disease, may back-fire. Furthermore, in severe hypertension, the use of mild drugs is potentially dangerous, giving the physician a sense of security while the disease continues relentlessly on its ravaging course.

There are no known late toxic reactions to protoveratrine. Immediate side effects are those attributable to vagal stimulation, i.e., nausea and vomiting. The rapid development of partial tolerance in a few hours, with restoration of sensitivity after a few hours rest, is unexplained.

Ganglionic blocking agents show many side effects, most of them the result of parasympatholysis or sympatholysis (Table V). Only two serious ones of this nature have been encountered. The first occurs when partial, often asymptomatic, obstruction to a hollow organ has been present. Complete obstruction may result. The second is concerned with the mode of excretion. Absorbed blocking agents are excreted in the urine. If severe renal disease is present, ganglionic blockade may cause hypotension and anuria; as the drug is then [illegible]

To set [illegible]

cologic of [illegible] unavailable in modern chemotherapy,

but sometimes it becomes necessary. The activity of cholinergic drugs is enhanced when ganglia are blocked; thus, urecholine and prostigmine provide useful tools in abating unwanted parasympatholysis (98). Likewise norepinephrine infusions combat the hypotension quite effectively.

TABLE V

SIDE EFFECTS OF GANGLIONIC BLOCKADE

Carotid Sinus Reflex	Decreased
Cardioaccelerator nerves	Blocked
Cardiovascular reflexes (cold pressor, etc.)	Blocked
Venous pressure	*Decreased*
Eye—Pupil	Fixed in mid-position
—Accommodation	Fixed at normal resting point
Ptosis	Slight or absent
Ear—Eustachian Tube	Paralyzed?
Salivary secretion	Decreased
Gastric juice, acidity and volume	Decreased
Gastrointestinal motility	Decreased
Gastric tone	Decreased
Colonic tone	Decreased
Defecatory Reflex	Decreased
Urinary Bladder tone	Decreased
Sweating	Decreased
Sexual potency (male)	Inhibited
Response to injected norepinephrine	Increased
Response to injected cholinergic drugs	Increased

Mecamylamine intoxication occurs *in azotemic* individuals and in others with poor renal function. It is characterized by gross, generalized coarse, muscle tremor, increased with activity, disappearing with sleep, by nervous tension and sometimes by visual hallucinations. The state resembles delirium tremens. The "flapping" tremor, which involves all voluntary muscles in advanced stages, is not associated with cog-wheel rigidity and only moderate hy-

perreflexia is found. The tremor usually remains for many days after discontinuation of the offending drug, even as long as two weeks. Severe hyperpyrexia, without infection, leading to death was observed once. Dilantin may partly ameliorate the condition. It is probable that this secondary amine of a camphor nature affects the central nervous system; camphor itself is convulsant and high doses of mecamylamine cause gross tremors in dogs. We have observed fine tremors occasionally when hexamethonium ion was used. Meprobamate can cause leucopenia.

"Ganglionic blockade disease" occurs in poorly treated malignant hypertension (93, 94, 5); it is characterized by excessive tachypnea, worsened in the sitting or standing position, diffuse or patchy roentgenologic changes in the lungs with few physical signs, and interstitial pulmonary fibrosis at autopsy. Almost all cases have exhibited azotemia (5); the microscopic findings are indistinguishable from "uremic pneumonitis." One patient recovered after the use of cortisone; the remainder died.

All of the antihypertensive agents with powerful actions can induce cardiovascular accidents, due to the nature of the arterial disease (atherosclerosis) often encountered and too sudden alteration of hemodynamics. Arterial thrombosis is the most serious, although it is rare. Such reactions are not true side effects of the drugs themselves but are inherent dangers in their overenthusiastic and careless use.

Summary: Because drugs acting specifically on the autonomic nervous system may affect the elevated blood pressure in human hypertension, we may assume that there can be a profound neurogenic component in some cases. This component probably is mediated via sympathetic nerves. Although the ideal counteracting agent is not avail-

able, certain tools can be used with varying results on the course of the primary *disorder*. All have side effects and most, late toxic reactions, which usually do not preclude their use provided careful attention is paid to the patient and his personal reactions.

Chapter IV

NEPHROGENIC EFFECTOR MECHANISMS

EVIDENCE FOR EXISTENCE OF OTHER EFFECTOR MECHANISMS

To this point we have inferred that mechanisms other than neurogenic account for much of the generalized vasospasm seen in severe hypertensive states. Although their natures are imperfectly understood, there is sufficient experimental and clinical data to warrant careful examination of several hypotheses which fit or do not fit the facts.

Most of the evidence for the existence of effector mechanisms other than neurogenic comes from experimental hypertension and from the wide variations in the acute or prolonged effects of drugs acting on sympathetic nerves. To take up the pharmacologic evidence, the following clinical observations are pertinent:

1. Early and mild hypertension responds well to simple measures and milder acting sympatholytic drugs; severe hypertension, little or not at all.

2. Extensive surgical sympathectomy, either lumbodorsal or subtotal, still leaves a sizeable proportion of patients as hypertensive as before, relieves a fair number completely, with the remainder improved to variable degrees.

3. Full therapeutic doses of ganglionic blocking agents or protoveratrine cause intermittent or sustained normotension in a few cases, a modified response in many and no appreciable effects (other than postural ones) in the more severe forms of hypertension.

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2. Extensive surgical sympathectomy, either lumbodorsal or subtotal, still leaves a sizeable proportion of patients as hypertensive as before, relieves a fair number completely, with the remainder improved to variable degrees.

3. Full therapeutic doses of ganglionic blocking agents or protoveratrine cause intermittent or sustained normotension in a few cases, a modified response in many and no appreciable effects (other than postural ones) in the more severe forms of hypertension.

4. Injection of tetra-ethyl ammonium ion causes transient falls of blood pressure to a "floor," this level being low in milder cases and rising as the disease progresses into severe stages. Only in cerebral edema does the floor fall (95).

5. Injections of hexamethonium ion in full doses cause variable responses, the estimate of the neurogenic component affected by the drug ranging from 100 to 15 per cent of the total elevation of blood pressure above normal. The less the fall after hexamethonium ion, the higher is the final blood pressure. There is a reciprocal relationship between neurogenic and "humoral" factors in maintaining the blood pressure high (53) (see Table XIX, p. 110).

THE NATURE OF THE OTHER MECHANISMS

Two processes can be hypothecated to explain these findings:

1. The arteries and arterioles become so sclerotic that a mechanical increase in peripheral resistance accounts for the sustained hypertension in the absence of neurogenic mechanisms. This explanation is incompatible with the anatomic and pharmacologic facts. While hypertension causes vascular lesions, they vary in intensity and degree throughout the body. Only late hypertension is associated with these lesions. Reduction in blood pressure of a degree sufficient to cause local ischemia in areas of severe vascular disease usually can be accomplished without such ischemic manifestations.

2. The arteries and arterioles are in a state of spasm which is not mediated through nervous mechanisms. This is the only tenable hypothesis. If so, several causes of the spasm must be examined:

a) Some organ is forming and discharging into the circulation abnormal substances, which either are strong

vasoconstrictors themselves, or which inhibit the destruction of normally circulating pressor substances.

b) Some organ is not destroying or excreting pressor substances normally present, so that they accumulate to form a new homeostatic level.

" c) Some organ is sensitizing the blood vessels to normally circulating pressor substances.

d) For some reason the arterial and arteriolar walls become edematous, thereby increasing peripheral resistance."

Probably all of these mechanisms can operate under different clinical circumstances.

The vast experimental and large clinical experience with hypertension induced by renal ischemia focuses attention upon the kidney as a mediating mechanism for that component of elevated arterial pressure which is not neurogenic in origin. The posterior pituitary, however, forms a pressor substance and the adrenal cortex can sensitize blood vessels to vasoconstriction; therefore endocrine mechanisms must also be considered (Chapter V). In this section we are concerned, however, with nephrogenic mechanisms.

First, the effects of sympathetic nervous discharges upon the renal circulation must be examined. Both emotional tension and catechol amines cause renal vasoconstriction, abolished in the case of the former by sympathectomy. Curiously enough, norepinephrine constricts, in so far as is known, only the renal circulation to a greater extent than other vascular beds. The hemodynamic profile is similar to that seen in hypertension, with efferent arteriolar constriction being dominant. Epinephrine produces the same renal profile. Therefore, increased neurogenic sympathetic tone can cause relative renal ischemia, but ischemia of no other known organ.

4. Injection of tetra-ethyl ammonium ion causes transient falls of blood pressure to a "floor," this level being low in milder cases and rising as the disease progresses into *severe* stages. *Only in cerebral edema does the floor* fall (95).

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a) Some organ is forming and discharging into the circulation abnormal substances, which either are strong

4. No renin or angiotonin can be found after several weeks of hypertension, although the enzyme is present at first. VEM in blood, however, increases with time to a plateau (103).

5. The oxygen consumption of the kidney may be reduced (104).

In kidneys removed from hypertensive rats and dogs, the following enzymatic alterations have been demonstrated:

1. Amino acid oxidation is reduced (104, 105), suggesting a general inhibition of oxidative enzymes.

2. Transamination is reduced in the presence of adequate pyridoxal phosphate (104), suggesting a depletion from renal tissue of apotransaminase.

3. Deamination of amines is reduced (104), suggesting depletion of monamine oxidase.

4. Succinic dehydrogenase and possibly cytochrome oxidase are reduced (105). All of these enzymatic alterations can be explained by loss of renal tissue consequent to prolonged ischemia.

✓ In man, the following changes have been measured:

1 Renal oxygen consumption is usually reduced (106, 107), reflecting the ischemia.

2 The urine is usually acid (108), reflecting, perhaps, the acidity of the cortex in ischemia.

3. There is a tendency for renal loss of sodium and some chloride (109, 110, 4), caused in the case of sodium possibly by the acidity producing loss of base.

4. The ratio of ammonia to titrable acid is lower than normal, influencing possibly the sodium-losing tendency of hypertensive kidneys (111).

5. Primary amines in arterial blood are usually elevated (90, 91, 112), a result, perhaps, of insufficient deamination from oxygen lack.

Removal of one ischemic kidney before hypertension

Second, what metabolic abnormalities are present in renal ischemia? This subject is little understood and alterations little measured. We know of some functional changes in experimental animals. Certain urinary abnormalities occur, reflecting what appear to be minor renal derangements. The cause is reduced blood flow, but whether it is mediated through oxygen lack or through some other mechanism concerned with flow remains to be discovered. In anaesthetized experimental animals the following occur after acute mechanical constriction of a renal artery:

1. Cortical oxygen tension falls, only to rise again without changing the constriction (96), suggesting intrarenal vasodilatation.

2. The same changes in blood flow take place. At this *point the renal vascular bed becomes sensitive to injected* epinephrine (97).

3. The cortex becomes acid (96).

4. Renin, the renal proteolytic enzyme, is released into renal venous blood, where it reacts with a globulin to form hypertensin or angiotonin, a constrictor peptide (99). Likewise, a vaso-excitor material (VEM) appears in blood (*100*). Angiotonin, produced by the ischemic kidney, can constrict the vessels of the kidney, making it more ischemic (101).

5. After several hours, blood pressure may rise in the experimental animal (97), probably due to the release of renin and/or pressor amines.

In the dog made hypertensive by partial constriction of a renal artery, the following changes have been seen:

1. Renal blood flow may be unchanged or decreased (102), but all of the increased resistance is not provided by the mechanical clamp; there is a component of intrarenal vasoconstriction as well, be it neurogenic or humoral (9).

2. Oxygen tension is lower than normal (96).

3. The cortex is acid (96).

This is more than an academic point. If hypertension were the result of chronic inhibition of a renal enzyme, removal of the enzyme or removal of the kidneys would accomplish the same result. The next question is whether a precursor is altered by ischemic kidney into a pressor

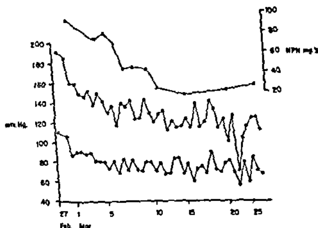


Fig. 7. Azotemic hypertension with reversal when azotemia regressed. Patient was a 45-year-old woman with abdominal lymphosarcoma which had involved both ureters, causing bilateral hydronephrosis. It was impossible to pass a urethral catheter through the left. Radiotherapy was instituted, resulting in a shrinkage of the tumor, a return of renal function toward normal and a fall of blood pressure, occasionally to hypotensive levels.

substance, or whether normal kidney inactivates a pressor substance found normally in blood. This question cannot be answered except by reference to the hypertension existing in the presence of one ischemic and one normal kidney. The hypotheses of best fit include both processes, "retention" hypertension developing with azotemia and

has persisted for long often relieves the elevated blood pressure. *Such experiments suggests that the ischemic kidney* was making something new, a pressor substance. At this point there are two apparently diametrically opposing viewpoints. Grollman's experiments show that totally nephrectomized dogs develop chronic hypertension when maintained by peritoneal dialysis or the artificial kidney. He therefore believes that healthy kidneys are necessary to maintain normotension (113). In other words, the kidney *destroys* normally circul [illegible] *on its removal (or in ische*[illegible] arising elsewhere, accumulate [illegible] the ischemic kidney *makes* pressor substances not normally present from precursors, adding something new. These two opposing theories can be resolved by moving to a more fundamental level.

The kidneys can make vasoactive amines from the proper amino acids. Perhaps by decarboxylation, without deamination, vasoactive peptides can be formed. Obviously, nephrectomized dogs cannot make these substances. In azotemia or in the absence of the kidneys, however, vasoactive amines are probably formed elsewhere and retained. The humoral substances produced by renal ischemia and those accumulating in the absence of the kidneys are different, although both are pressor. The latter are mainly catechol amines, for increased quantities *have been found in uremic blood and heart* muscle, urinary concentrations are low, and regitine and benzodioxane lower elevated blood pressure (as in pheochromocytoma) (38). A clinical counterpart is seen in cases of azotemic hypertension, where the blood pressure rises only with the blood nonprotein and falls when *azotemia* is relieved (Fig. 7). Prostatic obstruction is the most com*mon example.*

TABLE VI

AMINO ACIDS CAPABLE OF FORMING URINARY AMMONIA*

Amino Acid	*Renal Amino Acid Oxidase Present*	*Renal Deaminase Present*	(*Dog and Rat*) *Renal Decarboxylase Present*	(*Dog and Rat*) *Renal Amine Oxidase Present*
Glycine	+			
L-Alanine	+			0
L-Leucine			+	+
L-Cysteine			+	?
L-Methionine			?	?
L-Aspartic Acid	?		?	?
L-Asparagine				
L-Glutamine		+		
L-Histidine			+	+
Oxygen required for enzyme	+	0	0	+
No ammonia formed by glutamic acid, lysine or arginine				

* After Meister (432)

or diamine oxidase, which also acts on other diamines such as cadaverine. The remainder are oxidized by monamine oxidase.

Both of these enzymes are found widespread throughout many tissues. The liver is a rich source. Smooth muscle and gut contain them. Their ubiquitous nature is all out of proportion to their known metabolic functions.

The most interesting aspect of monamine oxidase in reference to renal ischemia is its sensitivity to oxygen lack (Fig. 8). Small decrements of oxygen tension inhibit enzymatic activity considerably, which is not always the case for other oxidases (89). If this relationship holds in

"production" hypertension of the ordinary renal or "essential" variety.

How are these often subtle changes made? What are the enzyme systems concerned? Very little is known, but speculation is rewarding.

The Amine Oxidase Theory: The kidney is an organ of high metabolic activity with one of the largest oxygen consumptions and blood flows of any in the body. Filtration is a passive process, tubular transport usually an active one. The kidney makes some ammonia from glutamine, thereby providing a base-conserving mechanism. Other amino acids undoubtedly contribute their nitrogen groups as well, probably by transamination or deamination.* There are many enzymes in kidney. Of them, decarboxylases of certain amino acids have been described; of tyrosine, histidine, dihydroxyphenylalanine (DOPA), tryptophane, leucine and 5-hydroxytryptophane. Decarboxylation is an anaerobic process, liberating carbon dioxide from the amino acid and leaving the amine residue.

We do not know for certain that amino acid metabolism takes place in the kidney primarily through decarboxylation (Table VI). The enzymes are found, however, and presumably must act. If they do, they can provide bicarbonate for tubular transport. Interestingly enough, most known decarboxylases are pyridoxal enzymes.

The amine residues of these amino acids are the vasoactive substances, tyramine, histamine, dihydroxyphenylethylamine, tryptamine, isoamylamine and serotonin. Histamine is deaminated by a special enzyme, histaminase

* *There is little or no L-amino acid oxidase in mammalian kidney.* Glycine oxidase is found, but for other amino acids to donate ammonia requires either transamination to form glutamine, or the two phase reaction, anaerobic decarboxylation and then oxidative deamination by monamine oxidase.

that passed would be distributed to all vascular organs and tissues, including brain, splanchnic bed and liver. In so doing, they would be expected to show 1) vasoactivity before being deaminated and 2) some stimulatory or depressant actions on cerebral metabolism.

Bacteria in the colon have the proper decarboxylating enzymes for these amino acids and for several others. The resultant amines should theoretically act on the vascular system and brain in a similar manner, if absorbed. That they do not usually so act can be explained by their destruction by amine oxidase in intestinal wall and in liver. For it is well known that primary amines and even epinephrine can be ingested in large quantities without systemic effects; adding one or more methyl groups to their side chains, as in amphetamine or ephedrine, however, prevents oxidation by hepatic and intestinal amine oxidase, allowing the drug to pass unchanged through liver and act on brain or blood vessels. No orally active amine vasoconstricting agent lacks this side chain. It is possible, however, that when bacterial flora are selectively inhibited by antibiotics, products of intestinal putrefaction can be absorbed into the circulation from the lower colon and cause symptoms, especially when the liver is damaged.

The fact that extracts of arterial hypertensive blood usually contain more primary amines than those of normotensive blood (90, 91), and that certain new or abnormal amines [illegible]

[illegible] states, such as shock and congestive heart failure, would be associated with the same metabolic abnormality.

This attractive theory, first propounded by Holtz (87), has received considerable attention from our group.

the living animal, we may readily conceive of the consequences of renal oxygen lack.

The amino acids decarboxylated by kidney would continue to be so metabolized. Oxidation of the amine res-

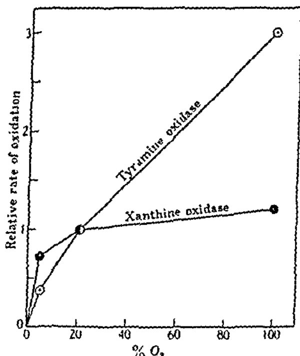


FIG. 8. Relative rate of oxidation as a function of oxygen tension. Dotted circles are for tyramine, or monamine oxidase, solid for xanthine oxidase. A reduction in oxygen tension of 50 per cent reduces the activity of the enzyme by about 50 per cent. Thus, monamine oxidase, as opposed to xanthine oxidase, is extremely sensitive to oxygen lack. (From Kohn, H. I.: Tyramine oxidase. *Biochem. J.*, *31*:1693, 1937.)

idues would be diminished in proportion to the oxygen lack. Presumably these amines would reenter the circulation through the renal vein and be deaminated by monamine oxidase at other sites where there is adequate oxygen. First, the lung would take some of them out; those

amines (which is theoretically possible), a minor vicious circle could be induced. The result would be minor degrees of fluctuating neurogenic hypertension and many of the symptoms of the neurogenic hypertensive state."

Since we are concerned primarily with the killing factor in hypertension, and not with mild neurogenic vasospastic states, it is well to examine the properties of this enzyme system further. There are two which are of help in implicating a disturbance of amine oxidation. First of all, amine oxidase acts on hypertensin or angiotonin (4, 112). This pressor amine is a complex polypeptide (119). Second, the enzyme acts on pherentasin. This pressor amine is probably a polypeptide (120). If the enzyme can act on terminal amines of peptides, it is possible that the formation of such peptidic amines occurs through decarboxylation and destruction by terminal amine oxidation. Therefore, we cannot exclude monamine oxidase in any theory of pathogenesis.

This enzyme probably needs vanadium as a cofactor. Vanadium occurs in three valence states and is therefore a good metal for oxidation-reduction reactions, being used as such by certain ascidia which concentrate it from sea water. While not shown to be an essential trace element for man, vanadium is found in tissues of mammals and occupies a place in the periodic table where essentiality might be inferred. This subject will be discussed further in Chapter VI.

Possible Role of the Lungs: In order to cover other conceivable mechanisms of vasospasm induced by humoral pressor substances, we cannot *neglect the* pulmonary circulation Any vasoactive material formed in an organ and discharged into the venous circulation must pass through the lungs before entering the area of action, the peripheral arterial bed. The lungs destroy at least one vasoactive

Partly purified but still crude amine oxidase, injected into rats, *prevents the pressor action* of both renin and pherentasin (*vide infra*). Furthermore, hypertensin or angiotonin is a good substrate for the enzyme (112, 116), indicating the presence of a primary amine group necessary for activity, for the reaction mixture is vascularly inert or depressor. Renal hypertensive dogs can be maintained normotensive on daily injections of the active enzyme (117, 112). All naturally occurring pressor substances are amines. Why, then, does not this enzymatic disturbance account fully for the establishment and maintenance of hypertension?

Perhaps it does, but not through the mediation of the substances listed. For all of them are relatively weak pressor amines when compared to norepinephrine. Very large quantities would be required to cause hypertension, amounts readily detectable in blood. Furthermore, a mixture of these amines would be expected to produce a peripheral circulatory profile different from that seen in hypertension, in so far as is known, for many of them have selective actions on different vascular beds (112), although all, including histamine, constrict the vessels of the kidneys (118). Therefore, circulating primary amines from simple amino acids cannot be implicated as direct causes of generalized vasospasm. They can be concerned, however, with some of the minor manifestations of hypertension, such as headaches, anxiety, tension, nervousness, insomnia, the diencephalic blush, flushing, sweating and the like. If they can cause nervous and emotional tension (which some of them can), and if nervous tension can cause peripheral vasoconstriction through sympathetic nervous discharges (which it can), and if sympathetic discharges can cause neurogenic renal ischemia (which it can), and if renal ischemia can produce circulating primary

ably is associated with renal abnormalities (90, 91, 120-124). As far as is known, it is the only pressor substance found so far in hypertensive blood but not in normotensive blood. There is more in arterial than in venous blood.

Pherentasin has a prolonged pressor action in rats, especially those with renal hypertension (91). It also constricts the smooth muscle of the isolated rabbit aorta (120). Because of its strong pressor action and the small quantities present, isolation and identification has been most difficult. Much of what is known of its nature comes from inactivation studies by known agents.

Pherentasin probably contains a trace metal essential for activity, the nature of which is unknown. It is inactivated by many antihypertensive agents not acting on sympathetic nerves (Table VII) and disappears from the blood when hypertension is controlled. No one knows how it is formed.

Renin: Now largely discarded, the mechanism for the formation of renin by ischemic kidneys supplied an attractive hypothesis to explain chronic renal hypertension. When the kidney is made ischemic, renin is released into renal venous blood from parenchymal tissues, possibly the juxta-glomerular apparatus (125). This proteolytic enzyme acts on an α_2-globulin made in liver, partially hydrolyzing it to hypertensin or angiotonin,* a vasoactive polypeptide. As with most other more simple substances, this pressor amine does not produce the peripheral circulatory profile of the hypertensive state, as does norepinephrine (126, 127). Unfortunately for the theory, renin and its effector substances have not been found in renal venous blood of dogs or human beings with chronic hypertension. They do appear, however, in the acute vasospastic states of acute

* Hypertensin and angiotonin are used interchangeably except when reference is made to a specific preparation. One term should be dropped.

material, serotonin, and probably others; for over a hundred years physiologists have taken advantage of this property to free shed blood of "spätgift" and "frühgift," constrictor and dilator substances, in preparation for perfusion experiments. Presumably monamine oxidase is the enzyme which deaminates constrictor primary amines in the pulmonary circuit.

Let us for a moment consider what might happen if all pulmonary monamine oxidase were inhibited. A portion of the pressor amines formed normally by kidney or tissues would be transported unchanged from venous to arterial circulations and would act on the peripheral blood vessels; the blood pressure would rise unless cardiac output were depressed. The remainder would constrict the pulmonary vascular bed, causing pulmonary hypertension. If *extra* quantities of primary amines were formed by kidney (or liver) and pulmonary monamine oxidase were inhibited, or saturated beyond its capacity to oxidize them, further vasoconstriction would result. Therefore, the pulmonary circulation could play a part in hypertension.

In this respect it is interesting that the lungs were the only organs in which Tipton detected vanadium, the possible cofactor of monamine oxidase. The pulmonary circulation responds to hypoxia by constriction. The lungs contain many abnormal trace elements, notably aluminum and titanium, a known enzyme inhibitor. This hypothesis *to our knowledge has not been explored.*

SPECIFIC EFFECTOR SUBSTANCES

Pherentasin: Although pherentasin has never been proven to come only from the kidney, this pressor amine of probable peptide nature is found in increasing quantities in the blood of patients with severe hypertension, is difficult or impossible to detect in mild stages, has been obtained from the renal vein of two patients, and presum-

TABLE VIII

Comparison of Properties of Animal Hypertensin and Human Pherentasin

Inactivation by	*Hypertensin* (1)	*Pherentasin* (2)	*Method and Remarks*
Drying	0	+	(1) can be lyophilized
Heat at pH 8 8	+	+	
Heat at pH 2 0	0	0	
Nitrous acid	+?	+	
Ninhydrin	+?	+	
Semicarbazide	?	±	(2) alters to a rapid reactant
Hydroxylamine	?	±	(2) alters to a rapid reactant
Amine Oxidase	+	+	
Tyrosinase	+	0	
Papain+cysteine	+?	+	
Chymotrypsin	+	0	
Carboxypeptidase	+	0	
Trypsin	+	0	
Pepsin	+	0	
Mg^{++}	0	0	
Mn^{++}	+	+	(1) rapid, (2) slow
Cr^{++}	?	0	
Co^{++}	+	±	(1) rapid, (2) partial
Fe^{++}	0	0	
V^{++++}	–	–	Both enhanced
Cu^{++}	0	0	
Zn^{++}	0	0	
Hydralazine	+	+	(1) more sensitive
NaSCN	+	+	
8-Hydroxyquinoline	+	+	(1) slow, (2) more rapid
EDTA Na_2H_2	0	±	(1) 50% in 22 hours (2) 50–100% in 3–6 hours
NaN_3	+	+	
$Na_2Fe(CN)_5NO$	+	+	Rapid for both
1-benzyl-2-methyl 5 methoxy tryptamine	+	+	Serotonin antagonist

Note: While distinct differences between these two substances are obvious, the hypertensin used was probably principally hypertensin I (angiotonin) obtained from hog renin and serum. Pherentasin may be hypertensin II of human origin with a slightly different structure, since there is no reason to believe that the α_2 globulins of pig and man are identical.

TABLE VII

INACTIVATION OF PHERENTASIN BY METAL IONS AND METAL BINDING AGENTS (120)

Estimated Activity, Per Cent of Control Values

Substance	*Immediate*	*4–5 hr.*	*24 hr.*	*Boiled after 24 hr.*	*Color Developed*
Mg^{++}	91	130	61	0	0
Cr^{++}	187	180	*12*	0	0
Mn^{++}	*45*	*17*	0	—	Pink cloudy
Fe^{++}	70	134	58	0	0
Co^{++}	59	50	50	0	Faint pink
Cu^{++}	96	107	*27*	0	0
Zn^{++}	84	137	54	27	0
Hg^{++}	168	51	115	0	0
None	100	100	100	80	0
Hydralazine	*46*	*20 (2)**	0 (18)		Deep blue
NaSCN	110	0 (1½)			Yellow-orange
$Na_2Fe(CN)_5NO$	110	0 (2)			0
NaN_3	89	0 (2)			*0*
8-Hydroxyquinoline	*35*	0 (1)			Pale green
Na_2H_2EDTA	100	0 (3)			0
Cysteine	100		100 (120)		0

All metals were added to the active material in 0.01 M concentrations, giving a final concentration in the 20 ml bath of 0.0005 M. The binding agents were added in 2–5 mg amounts per ml. extract. None of the metal ions alone affected the test system at 0.0005 M concentrations. The test method was that of Furchgott (85).

Figures in italics represent more than 50% inhibition.

* The figures in parentheses indicate the number of hours of incubation at room temperature when different from that shown at the top of the column.

renal ischemia, toxemia of pregnancy, shock, acute nephritis and congestive heart failure (128-131).

The validity of the renin mechanism is unquestioned as a defense reaction to acute and sub-acute circulatory changes. When these become chronic, renin is replaced by another vasospastic mechanism, probably that of pherentasin.

Pherentasin may be a form of hypertensin, for there are similarities between the two substances. There are also dissimilarities. The known properties of the two are listed in Table VIII. It is possible that metabolic alterations

animals to normal levels (132). It is not renin. As a protein, it probably acts enzymatically. Possibly sustained pressor principle is a precursor of pherentasin or represents another renal pressor mechanism.

Vasoexcitor Material: This unidentified substance has the property of sensitizing blood vessels to epinephrine when the latter is topically applied. It comes from ischemic kidney and is active in minute amounts. Larger quantities appear in chronic hypertension and congestive heart failure (100). Other substances, such as renin, pherentasin, sustained pressor principle and some primary amines, also have this property, which may be nonspecific.

Others: A great many vasoactive substances have been found in urine and blood, most of them eventually showing up as primary amines or more complex structures. They may represent metabolic by-products of the basic renal abnormality. No good case for any has been proven as directly concerned in chronic generalized vasospasm (133-135, 112, 4).

Comment. When many different substances are discovered or suspected to cause a single recognized abnormality, time usually leads to the abandonment of all but one as causative factors. Let us attempt to gather all of these different substances together and fit them into one unified scheme. To do so, we must speculate.

1. Renin may be involved in experimental renal hypertension. The evidence for this statement is indirect, in that anti-renin prepared by immunization reduces the hypertension of renal hypertensive dogs (136). Anti-hog renin neutralizes hog and dog renin and canine hypertension; anti-monkey renin neutralizes monkey and human renin and [illegible] ese anti-renins are there- [illegible]

[illegible] anti-monkey renin is found to affect human hyper-

occurring with time form the former from the latter, or that both have a common precursor. Hypertensin appears to require a metal as an activator.

Posterior Pituitary Factor: A pressor substance of polypeptide nature which has received some serious attention in hypertension is vasopressin. While a smooth muscle stimulant in small doses, it also has such antidiuretic properties that little speculation concerning its role in hypertension has been aroused. The direct relationship of the hypothalamus and the stalk of the pituitary, the known but minor electrolyte imbalances found, and the peptide nature of the substance make it not inconceivable as an effector substance, provided some minor alteration in its molecule negates its antidiuretic properties. While not a nephrogenic substance, one of its actions is on the kidney; if pressor, its release by the pituitary might be expected to cause widespread vascular constriction. The antidiuretic dose, however, is very small compared to the pressor dose. In our experience, even large amounts do not constrict the smooth muscle of the isolated rabbit aorta, as pherentasin and hypertensin do. Although it is possible that pherentasin may be a renal metabolic product of vasopressin, there is no proof or *disproof of this* idea. Interestingly enough, however, pitressin has been used to treat hypertension, with most variable and inconclusive results.*

Sustained Pressor Principle: A protein obtained from ischemic renal tissue or blood of animals in shock has the property of restoring the low blood pressure of pithed

* Pitressin or vasopressin may require an activator, for commercial preparations are inactive on the rabbit aortic strip. It exists in a ring form with an S-S linkage (435). We have attempted to activate it by adding copper, cobalt, ferrous iron, zinc, manganese, nickel and mercury, without *success save for an equivocable slight activation* with copper. Oxytocin or pituitrin is also inactive in this system.

contain a terminal amine group necessary for activity. Both can act as a VEM. Renin is inactivated *in vivo* by crude monamine oxidase (112).

6. Alterations may occur by two mechanisms, decarboxylation of a terminal carboxyl leaving a peptide amine or preferably peptide splitting leaving a terminal amine.

7. The substrates, as well as the renins, from different species are obviously different in composition. Human and primate renin will react with the substrates from all mammals tested, while animal renin will not react with α_2-globulins from primates. The exhibition of pressor activity of all hypertensins does not in any way mean that they are identical in chemical composition, but only that they have in common an active group, probably a terminal primary amine. Pepsin acting on casein produces a pressor peptide, pepsitensin, identical in action to hypertensin. There are thus many variables in species: the source of a renin, the source of serum α_2-globulins which almost certainly differ in composition from one species of animal to another, and perhaps the nature of the plasma enzyme converting the inactive peptide into its vasoactive form. The different amino acids found by various workers can be perhaps explained by the different sources from which the renin and its substrate were obtained (Table IX). Since human renin is unique to primates and since human globulins are unique to man, human hypertensin can be expected to be unique in its composition of amino acids. Therefore, human hypertensin may have only a moderate resemblance to that obtained from horses, dogs, pigs and cows, and could well be pherentasin.

8. There is no good evidence that renin or pepsin break down their protein substrates into substances having a terminal primary amine. Activation most likely occurs

tension, one can assume that renin or some similar protein is involved in human nephrogenic hypertension. But renin is found in renal venous blood only in acute vasospastic states and not in chronic hypertension, either experimental or clinical. Therefore, it must remain in the kidney, a highly speculative point.

3. Hypertensin or angiotonin is found only in acute vasospastic states. It has two forms, hypertensin I, inactive on isolated smooth muscle but active in blood,* and hypertensin II, a much more highly constrictor and pressor substance (138, 139). An enzyme in plasma converts I to II (141); apparently this is a metalloenzyme, requiring chloride and another metal which is tightly bound. Perhaps this enzyme is, or acts like, "sustained pressor principle."

4. Pherentasin is found only in chronic vasospastic states. Perhaps pherentasin is a form of hypertensin or angiotonin, altered either by a slightly changed renin, by a slightly different protein substrate, or by a new enzyme developing in chronic vasospasm, such as a peptide decarboxylase attacking the terminal carboxyl group.

5. Both of these substances are peptides inactivated by metal-binding antihypertensive drugs and therefore probably contain a metal necessary for activity. Both are inactivated by monamine oxidase and therefore probably

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* Hypertensin I obtained from the action of hog renin on horse serum contains the single amino acids aspartic, proline, valine, isoleucine, leucine, tyrosine, phenylalanine, arginine and two molecules of histidine (139). Peart, using hypertensin from rabbit renin and beef serum, disagrees slightly in that there was no isoleucine and two molecules of valine (142). Obviously tyrosinase inactivates both through the tyrosine portion of the molecule; amine oxidase attacks the terminal primary amine, probably on aspartic acid. Manganese inactivates by pseudopeptidase activity (140). The sequence of amino acids in Peart's hypertensin is Asp · Arg · Val · Tyr · Val · His · Pro · Phe · His · Leu (142b).

through a manganous peptidase (295). Thus, we can postulate several theoretical alternate reactions, based on all the evidence (Fig. 9, the active materials are in italics).

Reaction A would thus occur in acute vasospastic states, while reactions B, C, or D might take place in chronic states. Pherentasin needs no serum for activity; that it has at least six amino acids is based upon the findings of the active material showing six spots in chromatograms. A more unitary hypothesis is that pherentasin is actually hypertensin II, a matter on which we have no evidence as yet.

Comment: The pieces of the picture puzzle are falling into place, but there is need for much work to be done before the outlines are clear.

Locus of Action of Pressor Substances: While not directly established, it is reasonable to assume that all vascular smooth muscle is constricted by the pressor sub-

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A. Renin + α_2 globulin —Proteolysis→ Hypertensin I (peptide, 10 amino acids with terminal carboxyl?)

Hypertensin I + Plasma enzyme —Decarboxylation? / Peptidase (Mn^{++})→ *Hypertensin II* (active form with terminal amine) + CO_2

Hypertensin II + Monamine oxidase → inactive aldehyde + NH_3

Hypertensin II + Hypertensinase (plasma) —Peptidase?→ inactive substances

B. Hypertens[illegible]

[illegible] primary

D. Renin + different globulin —Proteolysis→ Pherentasin (6+ amino acids)
Pherentasin + Renal or plasma peptidase (Mn^{++}) → *Pherentasin* (terminal primary amine)

Fig. 9

TABLE IX

AMINO ACIDS IN VASOACTIVE PEPTIDES

Amino Acid	*Hypertensin*			*Vaso-pressin*	*Oxytocin*	*Pepsitensin*	*Common to All*
	*(142)**	*(139)†*	*(436)*	*(435)*	*(435)*	*(434)*	
Histidine	2	2	+				
Arginine	1	1		1		+	
Aspartic acid	1	1	+	1	1	+	Aspartic acid
Proline	1	1	+	1	1	+	Proline
Valine	2	1	+			+	
Lysine			+				
Leucine	1	1	+		1	+	Leucine
Isoleucine		1			1		
Phenylalanine	1	1		1		+	
Tyrosine	1	1	+	1	1	+	Tyrosine
Alanine			+			+	
Serine			+			+	
Glutamic acid			+	1	1	+	
Glycine			+	1	1		
Threonine							
Cystine				2	2		
Methionine							
No. amino acids	10	10	11	9	9	10+?	

NOTE: The differences in hypertensin may be due to the sources of the α_2 globulins from different species, hog, beef and horse. Vasopressin from hogs differs from that of beef in that leucine replaces arginine (435). Pepsitensin was obtained from casein (434).

* Rabbit renin+beef serum.

† Hog renin+horse serum.

to do more than detect the grosser lesions. A disease causing renal ischemia which then influences hypertension is often unsuspected because the cardiovascular manifestations of the elevated blood pressure may mask the underlying renal abnormality.

Organic Parenchymal Renal Disease: The most common diseases of the kidney producing ischemia are pyelonephritis and glomerulonephritis. The former [illegible] (143). The latter may be masked, insofar as the urinary sediment is concerned, by the superimposed hypertension. To list the other more unusual renal diseases, congenital or acquired, is hardly within the province of this discussion; most are often, but not always, associated with hypertension (144, 4).

Organic Extra-renal Arterial Disease: Atherosclerosis of the mouths of the renal arteries is common in generalized and in aortic atherosclerosis. The mechanism for the deposition of lipid in plaques about the orifices of bifurcating arteries is not known. Undoubtedly pressure changes play a part; possibly the presence of increased numbers of vasa vasorum at such bifurcations influence the lesions. Therefore, when atherosclerosis *involves the* renal arteries, partial renal ischemia may result with subsequent elevation of the blood pressure in predisposed individuals. With aortography becoming more common, such lesions are more frequently demonstrated. According to Blackman, they are the usual findings in hypertensive patients (145). It is possible that they represent the [illegible] (1[illegible], 147).

Because the existence of these lesions has not been

stance (or substances) responsible for the humoral component of sustained hypertension. If this is so, the following physiological alterations in vascular volume can be expected:

1. An increase in aortic volume, for the aorta is predominantly an elastic and not a muscular organ. As elastic limits are approached with increasing pressures, the rate of increase of volume lessens.

2. A decrease in the volume of blood in muscular arteries.

3. If veins also took part in the process, venous volume in the smaller muscular veins should be decreased, without, however, change in central venous pressure.

It is often difficult to detect the high pulse pressure in hypertension by feeling the dorsalis pedis arteries or even the radials. When blood pressure is lowered by hydralazine, the pulses in these smaller arteries become full. Thus, as pulse pressure falls, the detectable pulsations in muscular arteries increase. This seeming paradox is easily explicable on the basis that the muscles of these arteries are constricted in hypertension and that their volumes are diminished.

The high pulse pressure seen in most patients with hypertension is probably due to a relative loss of aortic elasticity because of stretching under pressure. Thus, the aorta becomes physiologically "hardened." In children and young adults we see low pulse pressures with diastolic hypertension, probably because their aortas are more elastic than are those of older people.

ANATOMICAL CAUSES OF RENAL ISCHEMIA

A variety of mechanisms and lesions can account for renal ischemia in man, many with experimental counterparts. Unfortunately our diagnostic methods are too crude

in the two groups. Yuile (158) recently reviewed the literature on the relation of obstructive lesions of the main renal artery and hypertension and concluded that such a relationship does exist in certain cases. This author pointed out the desirability of closer anatomical and physiologic correlation."

Organic Intra-renal Arterial and Arteriolar Disease: The almost universal lesion found in the kidneys of patients with hypertension at necropsy is renal arterial and arteriolar sclerosis. This lesion is not the cause of the hypertension, however, but is the result. And a late result, at that. About 50 per cent of patients having renal biopsies done during the operation of lumbodorsal sympathectomy had little or no arterial or arteriolar sclerosis (159). This lesion has been shown to result from hypertension produced by a variety of causes in rats (160-163), rabbits (164) and dogs (165, 7). Serial renal biopsies in dogs over a seven year period have demonstrated the gradual development of the lesions only after 2 to 4 years of both neurogenic and unilateral renal hypertension, the first sign being a thickening of the glomerular capsule and later an increase in material in the glomerular tuft staining with periodic acid (7).

None of these renal diseases alone can be said to cause hypertension in man, until azotemia develops. Hypertension is absent in 30 to 50 per cent of patients with the first two types in non-azotemic stages. The third type, of course, is the result of hypertension. They do, however, influence it profoundly and may often alter its course to a progressive and severe one. That quality which we call "the ability to react to stress by vasospasm" must apparently be present first and in conjunction in order for severe sustained hypertension to develop in patients with organic renal ischemia.

Why, then, are there no more "cures" of hypertension

emphasized in the recent literature, we quote from Braun-Menendez *et al.* in 1946 (148). "Goldblatt (149) was the first to show that hypertension was associated in some cases with sclerosis and narrowing of the orifice or of the lumen of the main renal artery. Leiter (150) somewhat later described a case of chronic hypertension associated with complete arteriosclerotic occlusion of the left renal artery and incomplete occlusion of the right. Freeman and Hartley (151) almost simultaneously reported hypertension in a patient who was nephrectomized because of an accident. At autopsy an atheromatous plaque was found to obstruct the mouth of the renal artery. Similar cases were described later by Blackman (145), Stewart (152), Saphir and Ballinger (153) and Laas (154). The importance of unilateral narrowing has been emphasized by Oppenheimer, Klemperer and Moschkowitz (146) who showed that in 18 cases who anatomically showed unilateral narrowing of the renal artery, 15 had hypertension. Blackman (145) found a narrowing of the renal artery at or near its mouth in 86 per cent of cases with hypertension. Richardson (155) recently reported stenosis of one or both renal arteries by arteriosclerotic plaques in 25 of 32 hypertensive patients studied at autopsy.

"Kahn and Laipply (147) observed a high incidence of bilateral arteriosclerosis in 1,000 hypertensive patients studied pathologically. Friedman, Moschkowitz and Marrus (156) observed arteriosclerosis of the renal vessels in 23 of 28 hypertensive patients who were nephrectomized.

"Lisa, Eckstein and Solomon (157) reported that in 100 consecutive cases coming to autopsy in which blood pressure readings were available, hypertension was present in 56 while 44 were nonhypertensive. No appreciable difference in the average diameter of the renal artery was found

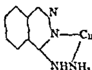
matter of fact, many effective drugs bind metals in one way or another (Chapter VI). This common property immediately focuses attention on metalloenzymes in kidney and vascular smooth muscle. It also stimulates considerable thought about the role of trace metals in pathogenesis of severe hypertension in which the neurogenic component has become of minor consequence.

The agents used in man are hydralazine and its derivatives, thiocyanate ion, sodium nitroprusside, 2,3-dimercaptopropanol (BAL), sodium azide and ethylenediamine tetra-acetate. Of practical interest for continuous use are only the first three, the effects of the other three being short-lived (Table X).

HYDRALAZINE AND OTHER CHELATING AGENTS

Hydralazine and its derivatives are unique drugs. No other agents known produce the same actions on vascular smooth musc[illegible] the key to [illegible] etiology of s[illegible] stood, a consideration of their pharmacological, chemical and enzymatic actions is necessary.

Chemical Reactions: Hydralazine, like other hydrazides, is a strong chelating agent. It will form a complex with iron, copper, tin, vanadium, manganese, nickel, silver and mercury. The possible structure is:



making a five-sided ring with nitrogen, a most stable chelate. This property is shared by isonicotinic acid hydrazide (isoniazid) and probably its isopropyl derivative

in cases of unilateral renal diseases subjected to nephrectomy? The answer is obvious. If hypertension, once long established, can cause bilateral renal arteriolar sclerosis, *removal of the one primarily affected* kidney will not remove *all* of the ischemic renal tissue. On the other hand, nephrectomy done in time may result in temporary or semi-permanent "cure" (166, 167). Experimental counterparts *of this situation* are known in rabbits, which get permanent hypertension after removal of an ischemic kidney which has been in place for three months or more (164); two of our unilateral renal ischemic dogs suffered *autonephrectomy, without* influencing their long-established hypertension.

Comment: These three types of organic renal disease can be considered as "accessory" factors in pathogenesis, but not primary ones. They probably do not cause hypertension in themselves without the neurogenic factor being present.

DRUGS ACTING ON NEPHROGENIC MECHANISMS

We can learn something about nephrogenic mechanisms from the actions of specific drugs, although the effective agents are few and have several actions. In experimental hypertension, however, there are broader leads. Three types of agents are active; metal binding agents, hydralazine and some other hydrazides (also metal binding agents), and pyrogens. The latter apparently dilate the renal vascular bed in some unknown manner, allowing greater *blood* flow and therefore counteracting renal ischemia.

Metal Binding Agents: All of the antihypertensive drugs used in man, which do not apparently affect neurogenic pathways, have in common the *ability to bind trace metals.* There are no known exceptions to this statement. As a

(iproniazid), whose pyridine bases in themselves weakly bind metals without the hydrazide group (Table XI). Distinct specificities for metals are exhibited, however.

Hydralazine is also a carbonyl reagent, as are some other hydrazides, phenyl hydrazine, for example, which forms an ozozone with glucose. It will bind pyruvate, acetate and acetaldehyde (168). Hydralazine has specific reactions, in that no ozozone is formed with glucose or lactic acid. It does not combine with any of the steroids tested (168). It is 1-hydrazinophthalazine (Apresoline).

This agent also complexes with the sulfhydryl groups on cysteine, glutathione, 2,3-dimercaptopropanol (BAL) and other simple mercaptans. The complex can be dissociated readily by arsenic.

TABLE XI A

ISONIAZID,* HYDRALAZINE AND METALS

	Isoniazid			
	Destruction by Me++ Autoclaving %	*Destruction by Me++ H_2O_2* %	*Binding of Hydralazine† + Me++* %	*Similarities*
Mg^{++}	0	5	0	+
Ca^{++}	0	5	0	+
Mn^{++}	100	100	87	+ Greatest at pH 6 5–7.0
Fe^{++}	50	80	22	
Fe^{+++}	70	95	100	+
Co^{++}	40	35	0	
Ni^{++}	10	15	48	
Cu^{++}	100	100	100	+ Greatest at pH 9.5–10 0
Zn^{++}	15	15	0	+

* Lewin, E., and Hirsch, J G.: Studies on the stability of isoniazid. *Am. Rev Tuberc & Pulm. Dis*, *71*:732, 1955

† Perry, H M, Jr., and Schroeder, H. A: Studies on the control of hypertension by Hyphex. III. Pharmacological and chemical observations on 1-hydrazinophthalazine. *Am. J. M. Sc*, *228*:396, 1954.

TABLE X

SUBSTANCES WITH METAL-BINDING PROPERTIES SELECTIVELY AFFECTING ARTERIAL HYPERTENSION (312)

Substance	*Rat*	*Dog*	*Man*	*Metals Bound*	*Reference*	*Remarks*
Thiocyanate		+	+	Many	173	Used in industry. CuSCN insoluble
Nitroprusside	+	+	+	Many	174	Zinc Reagent
Azide*	+	+	±	Many	175	Reactant
2,3-dimercaptopropanol (BAL)*	+	+	+	See Text	182	Chelator
Hydralazine and other hydrazines	+	+	+	See Text	168	Reactant
Tetrasodium pyrophosphate†	±			Many	4	Detergent and Reactant
9 mercaptans**	+	+ (2)		Many	182	Sulfhydryl binding
6 sulfur compounds	+			Several	182	SCNH most active
8-hydroxyquinoline	+			Many	183	Chelator
Perma Kleer	+				183	Polyamino carboxylic resin
Ca^{++} EDTA	+		±	Many	180, 183	Slight effect in man
Cr^{++} EDTA	+				183	But not chelates of Fe^{++}, Zn^{++}, Ni^{++}, Cu^{++}, Fe^{+++}
Mn^{++} EDTA	+				183	
Co^{++} EDTA	+				183	

* Short acting.

† Large doses. Only active phosphate of 11 tested.

** Ten others inactive; 5 nonspecific.

TABLE XII

INHIBITION OF HISTAMINASE BY HYDRAZIDES

Substance	Concentration Producing 50% Inhibition (molar)	Antihypertensive Effect
Guanidine HCl	10^{-3}	0
Thiosemicarbazide	10^{-4}	+
Semicarbazide HCl	5×10^{-6}	?
Hydrazine SO_4	8×10^{-7}	?
Aminoguanidine HCO_3	5×10^{-8}	0
1-4 dihydrazinophthalazine	2.3×10^{-8}	+
1-hydrazino-4-methylphthalazine	2.5×10^{-8}	+
1-hydrazinophthalazine	6×10^{-8}	+

Gross, F., Schuler, W., Tripod, J., and Meier, R.: Inhibition of diaminoxidase (histaminase) by phthalazine derivatives. *Experentia, 8*,229, 1952

Schuler, W. Inhibition of diaminoxidase (histaminase). *Experentia, 8*,230, 1952.

It binds strongly to arterial mash, serum proteins, egg albumin, and some polypeptides, possibly through carbonyl or sulfhydryl linkages. It does not bind with casein nor with mixed amino acids.

Enzymatic Reactions: Hydralazine is also an anti-enzyme for several known systems. It and its derivatives are strong antihistaminases, theoretically preventing histamine formed from histidine from being destroyed rapidly but not necessarily causing release of histamine from histidine (Table XII). Histamine can come from the action of histidine decarboxylase, believed to be a pyridoxal enzyme; if so, inhibition by hydralazine might be suspected. Hydralazine is a potent inhibitor of DOPA decarboxylase in small concentrations, also a vitamin B_6 enzyme (Table XIII). There is some evidence that histaminase itself may be a pyridoxal enzyme (169).

TABLE XI B

EFFECT OF METALS AND BINDING AGENTS ON HISTAMINASE (437)

(Substrate, Cadaverine)

Inhibition of Reaction %

Concentration	No Drug			Hydralazine			Isoniazid			Ba 12,630		
	10^{-3}	10^{-4}	10^{-5}	10^{-5}	10^{-6}	10^{-7}	10^{-3}	10^{-4}	10^{-6}	10^{-4}	10^{-5}	10^{-6}
Mn^{++}	8	0		0				50		0		
Fe^{+++}		0		0			0			0		
Co^{++}	0				50		0					50
Ni^{++}	0	0		50			20				50	
Cu^{++}		25	7	50				0		33		

Schuler, W., and Meier, R.: Releasing action of metals on the hydrazine-inhibited enzymatic oxidation of cadaverine. *Arch. Exper. Path.*, *223*.169, 1954

NOTE: The enzyme is inhibited by hydralazine, isoniazid and Ba 12,630, 2,4-di-hydrazinoquinazoline. The metals alone had little effect on the enzyme but inhibition of the enzymatic reaction by both hydralazine and Ba 12,630 was prevented by Co^{++} and Ni^{++}, that by hydralazine by Cu^{++}, that by isoniazid only by Mn^{++}, and none by Fe^{+++}. The reaction between drug and enzyme was irreversible, once it had occurred. These results offer indirect evidence for metal binding capacities of the three agents, although histaminase (diamine oxidase) is not known to require a metal for activity.

TABLE XIII—(*continued*)

Substance	*DOPA Decarboxylase Millimolarity of agent*				*Monamine Oxidase (Substrate, tryptamine) Millimolarity of agent*			
	10	*1*	*0.1*	*0.01*	*10*	*1*	*0.1*	*0.01*
Isoniazid	41	84	99	100	75	98	103	101
Iproniazid	108	—	—	—	14	*52*	91	101
Pyridoxal-Isoniazid	100	114	92	91 (90)	96	101	101	101
1-5 diphenyl-3-thiocarbo-hydrazide	100	97	—	—	—	—	—	—
8-hydroxyquinoline sulfonic acid	102	—	—	—	105	—	—	—
Reserpine	102	90	92	94	—	—	115	—
β-Mercaptopropionic acid	81	98	100	97	123	111	103	95
Tetrasodium pyrophosphate	86	101	97	—	95	—	—	—
Sodium cyanide	66	85	98	97	45	98	95	97
Sodium thiocyanate*	89	98	100	110	100	—	—	—
Sodium azide*	91	94	—	—	115	116	98	94
Choline azide*	100	—	—	—	112	104	101	101
Sodium Nitroprusside*	63	*71*	*76*	91	129	98	101	100

Italicized figures represent 20% change at 1 0 millimolar concentrations or less, considered significant.
Those in parentheses show further dilutions by 10.
* Antihypertensive in man. Note that some of these tend to depress one enzyme and enhance the other.

TABLE XIII

EFFECT OF METAL-BINDING AND ANTIHYPERTENSIVE AGENTS UPON TWO RENAL ENZYME SYSTEMS (GUINEA PIG)

(% Activity)

Substance	DOPA Decarboxylase Millimolarity of agent				Monamine Oxidase (Substrate, tryptamine) Millimolarity of agent			
	10	*1*	*0.1*	*0.01*	*10*	*1*	*0.1*	*0.01*
1-hydrazinophthalazine C-5968* (Hydralazine)	12	*23*	*59*	88 (99)	163	*159*	118	103
1-4 dihydrazinophthalazine C-7441* (Nepresol)	5	*21*	*21*	*66* (83) (100)	144	*156*	118	103
3-hydrazine-6-phenyl diazine C-6084*	4	*39*	*74*	87 (89) (90)	87	118	95	93
1,4 dihydrazinopyridazine C-13504*	20	*33*	*61*	102	25	82	98	84
Phthalazine C-7182	87	—	99	98	61	103	101	96
1-hydrazino isoquinoline · HCl C-7406	20	*42*	*76*	97	49	103	98	102

TABLE XIV B

EFFECT OF ADMINISTRATION OF HYDRALAZINE ON URINARY EXCRETION OF 4-PYRIDOXIC ACID (MG)* (111)

	No Subjects	*No Tests*	*Mean Before*	*No Tests*	*Mean During*	*Dose of Hydralazine*
Begun on Hydralazine	4	9	24.5 *(17.3–33.5)*	18	13.5 *(11.2–23.2)*	150–600
On Hydralazine for 1–3 Years	6			28	12.8 *(5.5–18.7)*	200–600
On EDTA†	3	10	22.1	15	24.0 *(22.0–26.0)*	
On EDTA and hydralazine	4			22	12.7 *(4.4–18.8)*	200–600
Normal	5	22	21.8			
Atherosclerosis	4	22	27.4			

* Per 4 hours after 50 mg. orally of pyridoxal hydrochloride
† Calcium disodium ethylenediamine tetraacetate intravenously
The ranges for each group, shown in italics, are the mean excretion rates of each patient

[illegible]

the specificity of the hydralazines for a reaction not exhibited by other hydrazides and similar agents.

The known actions of hydralazine are listed in Table XV. The actions of a large number of similar substances are shown in Table XIII as regards the two enzyme systems considered here.

Other Metal Binding Agents: Thiocyanate ion is used in industry for making soluble salts of a number of metals. In man, according to Sollmann (173), it "hastened the elimination of metals, perhaps by rendering the metal-protein compounds more soluble." In Table XVI is a partial list of the soluble metallic salts of thiocyanate. Symptoms

Whether or not hydralazine causes excretion or deficiency of vitamin B_6 is not known. It does seem to interfere with the conversion of pyridoxal to its metabolite, 4-pyridoxic acid (Table XIV). A relative, isoniazid (isonicotinic acid hydrazide), promotes the excretion of a pyridoxal-isoniazid complex in urine and can cause peripheral neuritis in patients taking large amounts for tuberculosis; presumably the neuritis is due to vitamin B_6 deficiency (170). Isoniazid is a good inhibitor of DOPA decarboxylase and a poor one of monamine oxidase (Table XIII). Its derivative, iproniazid (isonicotinic isopropyl hydrazide) does not affect DOPA decarboxylase but is a strong inhibitor of monamine oxidase. Both inhibit histaminase (171, 172). The latter cannot be used clinically because of its "benzedrine-like" reactions of euphoria and cerebral stimulation, believed to be due to cerebral and peripheral inhibition of this oxidase, thus allowing natural primary amines to circulate.

We are discussing these related hydrazides because of their similarities of structure, their antienzymatic activities, their affinities for vitamin B_6 and their abilities to

TABLE XIV A

EFFECT OF REPEATED ADMINISTRATION OF PYRIDOXAL HYDROCHLORIDE UPON EXCRETION OF 4-PYRIDOXIC ACID (MG.) (111)

Subjects	*No.*	*Mean Total Dose Vitamin B_6 (mg)*	*Mean Days Given*	*Amount Excreted on Last Test*	
				Mean	*Range*
Normal	5	250	5	22 3	9.8–27 8
Atherosclerosis	4	250	5	27 8	21.8–32.4
Patients on EDTA†	3	1470	18	21.0	18 0–24 2
Patients on Hydralazine	11	700	12	11.3	2.6–20.5

TABLE XIV B

EFFECT OF ADMINISTRATION OF HYDRALAZINE ON URINARY EXCRETION OF 4-PYRIDOXIC ACID (MG)* (111)

	No Subjects	No Tests	Mean Before	No Tests	Mean During	Dose of Hydralazine
Begun on Hydralazine	4	9	24 5 *(17 3–33.5)*	18	15 5 *(11.2–23.2)*	150–600
On Hydralazine for 1–3 Years	6			28	12 8 *(5.5–18.7)*	200–600
On EDTA†	3	10	22 1	15	24 0 *(22.0–26 0)*	
On EDTA and hydralazine	4			22	12 7 *(4.4–18 8)*	200–600
Normal	5	22	21.8			
Atherosclerosis	4	22	27.4			

* Per 4 hours after 50 mg orally of pyridoxal hydrochloride.
† Calcium disodium ethylenediamine tetraacetate intravenously
The ranges for each group shown in italics, are the mean excretion rates of each patient

chelate trace metals. The pati[illegible]
not ant[illegible]
of ison[illegible]
the specificity of the hydralazines for a reaction not exhibited by other hydrazides and similar agents.

The known actions of hydralazine are listed in Table XV. The actions of a large number of similar substances are shown in Table XIII as regards the two enzyme systems considered here.

Other Metal Binding Agents: Thiocyanate ion is used in industry for making soluble salts of a number of metals. In man, according to Sollmann (173), it "hastened the elimina[illegible]
prot[illegible]
list[illegible] soluble metallic salts of thiocyanate. Symptoms

TABLE XV

SUMMARY OF PROPERTIES OF HYDRALAZINE OTHER THAN CARDIOVASCULAR

Basic Chemical Reactions In Vitro	*Reference*
Metal binding	
complete for Fe^{3}, Cu^{2}, Sn^{2}, V^{5}	(168)
partial for Mn^{2}, Fe^{2}, V^{4}, Ni^{2}, Ag, Hg	
none for Na, K, Be^{2}, Mg^{2}, Ca^{2}, Zn^{2}, Co^{2}, Cr^{3}, Cd^{2}, Al^{3}, As^{3}, Pb^{2}	
Carbonyl reagent	
with pyruvate, acetaldehyde, acetate	(168)
not with glucose, lactic acid	
Complex with *SH*	
with cysteine, glutathione, BAL and other simple mercaptans	(168)
Protein binding	
with serum, arterial mash, egg albumin, polypeptides	(436)
not with casein, mixed amino acids	
Enhances	
monamine oxidase (10^{-4})	(Table XIII)
Anti-enzyme	
for histaminase (10^{-6}), stronger than guanidine, thiosemicarbazide; weaker than hydrazine, aminoguanidine; equal to semicarbazide	(172)
for DOPA decarboxylase, moderate (10^{-4})	(Table XIII)
for succinic dehydrogenase, cholinesterase, polyphenol oxidase, none	(111)
Combination with	
no primary amines or simple amino acids	
lyophilized angiotonin	(168)
Blocking Actions In Vivo	
Weak for epinephrine, norepinephrine, arterenone, tyramine, isoamylamine, angiotonin	(168)
Strong for pherentasin, pervanadyl, cadmium, barium, pitressin	(168, 438)
Variable for serotonin according to species (weak in rat and dog, strong in cat)	(168, 63)
Blocking Actions on Rabbit's Arterial Strip	
Strong for pherentasin, angiotonin	(120)
Weak for norepinephrine and other primary amines	(120)

TABLE XV—(*continued*)

Vascular Reactions in Animals	*References*
Dilates constricted vessels, renal, femoral, coronary; acts for many hours	(438)
Does not dilate dilated vessels further (as in spinal animal)	(438)
Abolishes constriction caused by Ba, pitressin, ephedrine, ergotamine, histamine, Privine	(438)
Reactions in Man	
Lowering of plasma cholesterol	(180)
No lowering of blood pyruvate or total carbonyl	(168)
Apparent loss of Ti in urine	
Mild anemia	(168)
? Histamine release	(172)
Increases cardiac output, tachycardia	(425)
Increases renal plasma flow	(426, 427)

and side effects due to this ion are variable, but resemble in some respects those induced by hydralazine; because of the dissimilarity of the chemical structures of the two

TABLE XVI

SOLUBLE COMPLEXES OF THIOCYANATES IN WATER

Soluble	*Partly Soluble*	*Insoluble*
Mn	Pb	Cu
Fe	Hg	Ti ?
Co	Ag	Si
Zn		
Mo		
Ca		
Sr		
Ba		

Hodgman, C. D., ed.: *Handbook of Chemistry and Physics*, 33rd Ed. Cleveland, Chemical Rubber Publishing Co., 1951.

TABLE XV

SUMMARY OF PROPERTIES OF HYDRALAZINE OTHER THAN CARDIOVASCULAR

Basic Chemical Reactions In Vitro	*Reference*
Metal binding	
complete for Fe^3, Cu^2, Sn^2, V^5	(168)
partial for Mn^2, Fe^2, V^4, Ni^2, Ag, Hg	
none for Na, K, Be^2, Mg^2, Ca^2, Zn^2, Co^2, Cr^3, Cd^2, Al^3, As^3, Pb^3	
Carbonyl reagent	
with pyruvate, acetaldehyde, acetate	(168)
not with glucose, lactic acid	
Complex with SH	
with cysteine, glutathione, BAL and other simple mercaptans	(168)
Protein binding	
with serum, arterial mash, egg albumin, polypeptides	(436)
not with casein, mixed amino acids	
Enhances	
monamine oxidase (10^{-4})	(Table XIII)
Anti-enzyme	
for histaminase (10^{-6}), stronger than guanidine, thiosemicarbazide; weaker than hydrazine, aminoguanidine; equal to semicarbazide	(172)
for DOPA decarboxylase, moderate (10^{-4})	(Table XIII)
for succinic dehydrogenase, cholinesterase, polyphenol oxidase, none	(111)
Combination with	
no primary amines or simple amino acids	
lyophilized angiotonin	(168)
Blocking Actions In Vivo	
Weak for epinephrine, norepinephrine, arterenone, tyramine, isoamylamine, angiotonin	(168)
Strong for pherentasin, pervanadyl, cadmium, barium, pitressin	(168, 438)
Variable for serotonin according to species (weak in rat and dog, strong in cat)	(168, 63)
Blocking Actions on Rabbit's Arterial Strip	
Strong for pherentasin, angiotonin	(120)
Weak for norepinephrine and other primary amines	(120)

Sodium azide, which has a strong affinity for metals, is a rather transient vasodilator, as is its relative, choline azide, producing sharp reductions in blood pressure. It is said to show differential actions in normotensive and hypertensive rats, not depressing blood pressure in the former (175). We have been unable to confirm claims for chronic effects in man.

British Anti-Lewisite (2,3-dimercaptopropanol, BAL) is used clinically to remove trace metals from the body. Much is known of its actions (176, 177, 178), which do not include affinities for all metals. It is a disulfide chelating agent. In our hands, it has proven effective in causing lowering of blood pressure in American hypertensive patients for periods of a few hours. On the other hand, British patients have responded with a rise. It is prolongedly pressor in normotensive subjects (177) but was depressor in one American hypertensive patient in the hands of others (176). BAL has little clinical use at present in hypertension. In cadmium poisoning, it will mobilize the metal, but binding is weaker than is that of kidney, for the metal is deposited and cadmium nephritis results (179). Many other heavy metals are mobilized and removed in the urine.

Ethylenediamine tetra-acetate is a mild antihypertensive agent in man. Given intravenously as the disodium calcium complex, it either lowers elevated blood pressure or reduces the patient's requirement for ganglionic blocking agents (180). Not a strong chelating agent for many metals, it has little clinical use at present. Prolonged oral use has led to no toxicity; intravenous use has produced signs of zinc deficiency (181), which resembles that of vitamin B_6.

Experimental Compounds: In anaesthetized rats and other animals, a number of compounds having the capacity for binding or chelating trace metals lower hypertensive

agents, a common denominator must be present in the actions of both (Table XVII). Little interest in its mode of action has been aroused. It can inhibit a number of enzymes, such as zinc-containing carbonic anhydrase and amino acid oxidase (173b). It is antithyroid; all antithyroid agents except those which act by competitive inhibition bind metals.

Sodium nitroprusside is an antihypertensive agent of considerable potency when given intravenously; alterations in the course of the disease have been described (174). A zinc reagent, it is a strong metal binder. Its chronic toxicity is not known but should become apparent with continued use.

TABLE XVII

SIDE EFFECTS OF TWO METAL-BINDING ANTIHYPERTENSIVE DRUGS (84, 108)

	NaSCN	*Hydralazine*
Action		
in normotension	0	±
in renal hypertension	+	+
enhanced by sympathectomy	+	+
Arthralgia	+	+
Lupus-like syndrome		+
Cholesterolysis	+	+
Rhinitis	+	+
Conjunctivitis	+	+
Anti-thyroid	+	0
Peripheral neuritis	+	+
Paraesthesias	+	+
Skin lesions	+	+
Headache	+	+
Flushing	0	+

both types of animals. D. Lowering of blood pressure in both types of rats, and depression of the pressor action of norepinephrine. E. Lowering of the blood pressure of both normotensive and hypertensive rats without greater effect on the latter and without altering the pressor action of norepinephrine (Fig. 11).

Mercaptan compounds which showed specific antihypertensive but not sympatholytic effects (Type A) in the rat were:

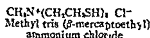


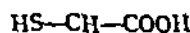


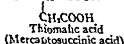


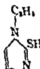


Procaine Salt of β-mercapto-propionic acid









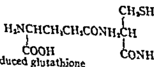
1-ethyl-2-mercaptoimidazole

Compounds showing both antihypertensive and norepinephrine blockade (Type C) were:



β-mercaptopropionic acid

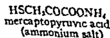








and to a less extent



blood pressure but do not affect or raise normal blood pressure.

Theoretically there are five types of sustained depressor responses of the blood pressure of hypertensive and normotensive rats to the intravenous injection of various active compounds: A. Little or no effect on normotensive rats with specific lowering of the blood pressure of renal hypertensive rats, while the pressor action of norepinephrine is unaltered or little affected (Fig. 10). B. Little effect on blood pressure with depression of the pressor action of norepinephrine in both types of rats. C. Effect of type A with depression of the pressor action of norepinephrine in

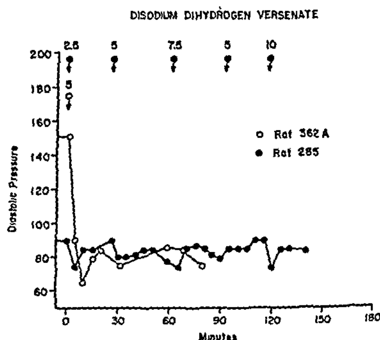
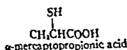


Fig. 10 Effect of intravenous EDTA on diastolic blood pressure of anaesthetized rats. Note that the normotensive pressure varies little, while the renal hypertensive falls with smaller doses. Typical type A response.

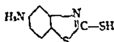
Certain mercaptans were depressor in both types of animals (Type E), although the last two showed significant differential activities:



α-mercaptopropionic acid



Monothioglycerol



6-amino-α-mercaptobenzothiazole



2,3-dimercaptopropanol (BAL) (Fig. 12)

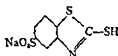
Only four mercaptans were sympatholytic (Type B) without depressor effects, the last to a lesser degree:



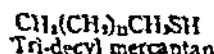
Acetonyl mercaptan



1-thio-2-hydroxy propane



Sodium-2-mercapto-5-benzothiazole sulfonate

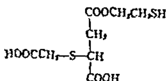


Tri-decyl mercaptan

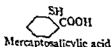
Five were inactive or pressor, the last having a short-lived differential action:



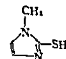
Cysteine



2-mercaptoethyl hydrogen (carboxymethylmercapto) succinate



Mercaptosalicylic acid



Tapazole



Pantetheine

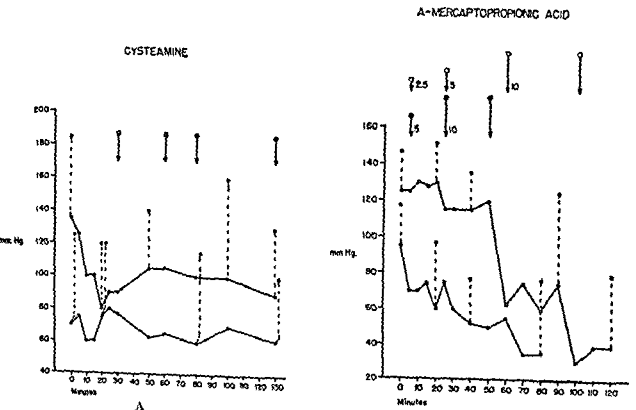


FIG. 11. Effect of intravenous sulfhydryl compounds on the diastolic pressures of anaesthetized rats. A. Cysteamine, 5.0 mg. Only hypertensive pressure is depressed (Type A). B. α-Mercaptopropionic acid. Both types of pressures are depressed (Type E). β-Mercaptopropionic acid gave a type A response. The dotted lines denote the rises after 0.5 γ norepinephrine. The dose of cysteamine at 0 minutes was 5.0 mg.

A group of sulfur-containing compounds were similarly divided; Type A activity was demonstrated by:

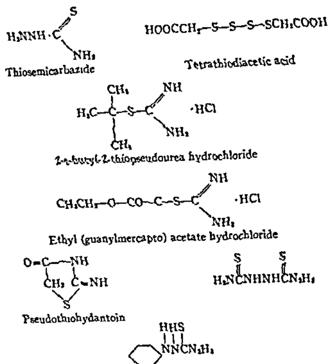
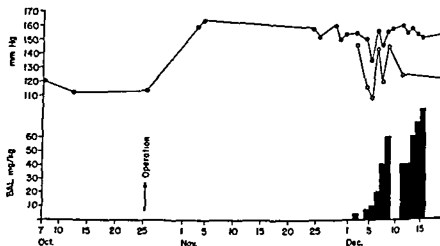


FIG 12. A. Transient effect of 2,3 dimercaptopropanol (BAL) on systolic pressure of renal hypertensive rat. Blood pressure was measured by the foot cuff method using a photoelectric cell. The open circles are measurements made 2, 3, and 4 hours after the injection, the closed circles 24 hours later. Note increasing "tolerance."

B. Effect of BAL on blood pressure of a 59-year-old patient receiving hydralazine (5968) and hexamethonium chloride (C_6) in too low doses to produce normotension. Doses are indicated at the top. BAL, 50 mg. every four hours intramuscularly was given for four doses. At the bottom, urinary excretion of hexamethonium ion and hydralazine are shown. The solid black areas represent free urinary hydralazine, the open areas that bound to sulfhydryl. All excreted hydralazine was bound after BAL was given. (From Perry, H. M., Jr., Schroeder, H. A., and Morrow, J. D.: *Am. J. M. Sc.*, 228:405, 1954)

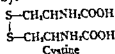


A

B

FIG. 12. *(See facing page for description)*

There was no activity exhibited by oxidized glutathione, nor by:



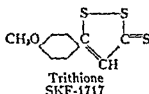


One compound of interest contained three ethyl mercaptans on a quaternary ammonium nitrogen; it was made on the possibility that ganglionic blockade as well as mercaptan effect might result. However, it acutely raised the mean diastolic pressures of normal and hypertensive rats 36 and 15 mm. Hg respectively, producing the usual differential mercaptan effect of a depression of 6 and 32 mm. respectively at the end of 2 hours. Another of special interest had the basic structure of hexamethonium ion with an ethyl thiopseudourea group on each quaternary nitrogen. Although listed as Type E, it depressed the mean diastolic pressure of 5 normal rats 36 mm. Hg and that of 5 hypertensive rats 86 mm. in doses of 1.0 to 1.5 mg. Possibly ganglionic blockade was combined with another action on the renal pressor mechanism.

Examination of the structures reveals that antihypertensive or depressor activity was confined to those aliphatic compounds having a terminal sulfhydryl group or SCNH in the molecule unencumbered by a heavy salt; aromatic compounds containing SCN were likewise active. Such compounds usually bind metals, sulfur-nitrogen binding being strongest with Cu, Ni, Ag, Cd and contiguous heavier elements in the periodic table. These results suggest that possibly some copper enzyme was altered or inactivated, causing the pharmacological activities of the compounds (182).

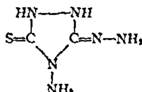
If this surmise be true, the next step was obviously to test known chelating agents in the same system, preferably those not metabolized. If they were active, obviously a metalloenzyme was altered.

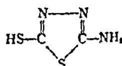
Type C activity was shown by only one:

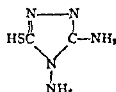


Trithione
SKF-1717

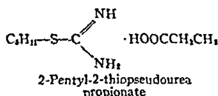
Partial sympatholytic with good antihypertensive activity was exhibited by:





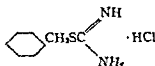


Type E activity occurred after the following, the last two showing differential effects:

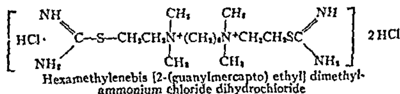


2-Pentyl-2-thiopseudourea propionate





2-Benzyl-2-thiopseudourea hydrochloride



Hexamethylenebis [2-(guanylmercapto) ethyl] dimethylammonium chloride dihydrochloride

In order further to control the studies, various pyridoxylidene metal amino complexes were subjected to the same test. Selective Type A effects were observed with the copper tyrosine, nickel arginine, aluminum phenylalanine, and possibly the cobalt phenylalanine complexes. No ef-

DIVALENT METAL DISODIUM ETHYLENE DIAMINE TETRA-ACETATE

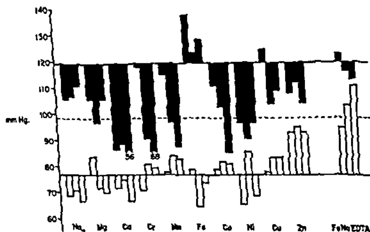
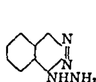


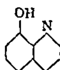
FIG. 13. The effects of a series of [illegible]
ethylene-diamin [illegible]
of hypertensive [illegible]
tized rats. The [illegible] metal complex represents the change 20 to 30 minutes after one intravenous injection of 5 mg; the second and third changes a like interval after subsequent injections. Mean changes are shown, each group representing at least 3 and usually 4 or more rats. All complexes were dihydrogen metal except for ferric as shown on the right. Note the comparable differences in hypertensive (mean diastolic pressure 119 mm. Hg) and normotensive animals (mean diastolic pressure 77 mm. [illegible]

[illegible] 1955)

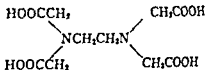
Activities of Type A were shown by the strong chelating compounds:



Hydralazine



8-hydroxyquinoline



Ethylenediamine tetraacetic acid (EDTA)

and Perma Kleer, a polyaminocarboxylic acid resin with chelating qualities. Pressor activity was exhibited by the weaker chelating agent, 1-6-tolylbiguanide. Therefore one or more metals must have been removed, presumably from metalloenzymes, since EDTA, at least, is not metabolized.

In order to ascertain which metal or groups of metals might be chelated, advantage was taken of the different stability constants of EDTA and various metals of the first transitional series. Figure 13 shows the results and Table XVIII the stability constants. Any metal removed from tissues must have displaced one with a lower stability constant. Aside from the ferrous chelate, which readily oxidizes to ferric in solution, it is evident that those with higher constants than 16.1 (for cobalt) are not active; these included the nickel, zinc and copper chelates. Since nickel has no known function, it is reasonable to assume that ferric iron, zinc, or copper was displaced from tissues by the chelating compound.

In order to determine whether or not the metal ions themselves showed activity, small amounts of the chlorides were injected (Fig. 14). Only ferrous, cobaltous, cupric and zinc were active. Cobalt is a known vasodilator, and zinc salts cause flocculation of plasma proteins, which may have accounted for the obscured effects. Suspicion therefore rests upon copper or zinc as being involved in the maintenance of renal hypertension in the rat.

pressure of 4 hypertensive patients, monothioglycerol was apparently inactive, a trithione (SKF-1717) given orally appeared inert. BAL, however, exhibited depressor activity in 6 hypertensive patients when given every 4 hours in doses up to 5.0 mg. per Kg.; the effects were relatively short-lived (2 to 4 hours). We did not observe a pressor effect after this material was given (183).

Comment: This common denominator of the antihyper-

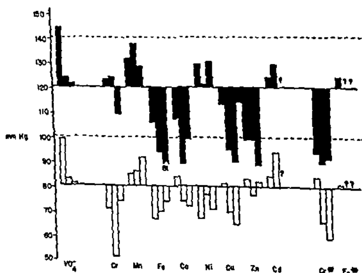


FIG 14. The effects of a series of metal ions on the diastolic pressures of groups of hypertensive
normotensive (mea
similarly treated. D
calcium salts were
indicated as well a
and chromic chlorides.
Note the differences between the ions and their
in Figure
nickelous,
Schroeder,
46.416, 19
Med,

TABLE XVIII

SIGNIFICANT EFFECTS ON DIASTOLIC BLOOD PRESSURE OF METAL CHELATES (15 MG.) AND ION (0.6 MG) IN HYPERTENSIVE RATS

Me^{++}	Atomic No.	Log K_1	$H_2MeEDTA$ (mm Hg)	$MeCl_2$ (mm Hg)
Na_2	11	1.66	—	—
Mg	12	8.69	—	—
Ca	20	10.59	−63	—
Cr	24	13.00	−51	—
Mn	25	13.47	−31	—
Fe	26	14.22	—	−40
Co	27	16.10	−33	(−21)
Zn	30	16 58	—	−29
Ni	28	18.45	(−22)	—
Cu	29	18.38	—	−28
$Fe^{+++}Na$		25.00	+33	—

Log K_1 is an index of the stability of the chelate, the higher values being more stable. The figures were taken from Sequestrene, a publication of the Alrose Chemical Co., Providence, quoting Scharzenbach *et al.* That for chromous is not exactly known.

EDTA—ethylenediamine tetraacetate.

fects were observed with three glutamic acid and two *phenylethylamine complexes. Copper* again comes under suspicion.

These same effects were observed in renal hypertensive dogs, by the use of BAL and hydralazine (Fig. 15). In renal hypertensive dogs BAL (5 mg. per Kg.) injected intramuscularly produced definite but transient (2- to 6-hour) depression of blood pressure, as did sodium thioglycolate intravenously. When BAL was injected with 1-hydrazinophthalazine, a moderately active depressor substance, the effects were enhanced. Only four of these compounds were sufficiently studied to give to human beings. Cysteine caused no demonstrable alteration in the blood

tensive compounds not acting on nerves, that is, the ability [illegible]

tion, their dispersing powers and their transport to other sites. The striking coincidence, however, of metal-binding properties and effect lead to only one conclusion; that one or more metals are bound and cleared from [illegible]

consideration of how they may act will be discussed in following chapters.

THE EFFECT OF ANTIHYPERTENSIVE AGENTS ON NEPHROGENIC EFFECTOR SUBSTANCES

A method for screening antihypertensive agents involves the isolated rabbit aortic strip, a spirally cut piece of smooth muscle which contracts when pressor substances are applied (120). Substances acting mainly on norepinephrine and other primary amines, acting on more complex pressor substances, and showing general inhibition of all types can be evaluated. While many agents tested cannot be applied to man, their activities can be evaluated readily on isolated muscle and in the hypertensive animal. A substance which is nontoxic, inhibits pherentasin, and lowers the blood pressure of hypertensive rats while not affecting normotension is obviously of therapeutic interest.

Pherentasin: Using the isolated rabbit aorta suspended in oxygenated Ringer's solution, a number of these substances have been tested for their activities against pherentasin. The relative degrees of inhibition are indicated in Table VII. All of the metal binding agents are inhibitory. On the possibility that pherentasin may be an adrenergic agent, a number of sympatholytic substances

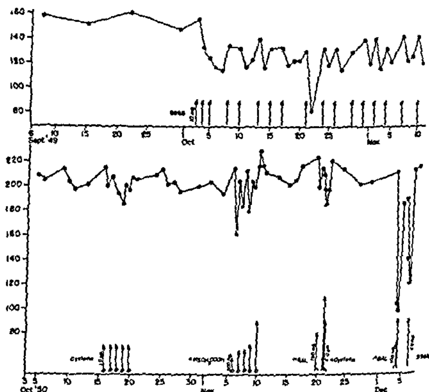


FIG. 15. Effect of various substances on the mean blood pressure of a ... as constricted in ... 1-Hydrazinoph- ... fect when given at less frequent intervals than daily, blood pressure falling for 24 hours and then rising in 48. Only small doses were required. During the subsequent year mean blood pressure rose. *Lower:* Cysteine intravenously caused only insignificant variations, sodium thioglycolate more pronounced but transient ones, BAL intramuscularly *alone* and combined with intravenous cysteine similar depressions but BAL combined with 5968 produced marked responses. Both the immediate (2- to 6-hour) and late (24-hour) responses to these substances are shown. Only BAL and 5968 together produced significant depression for 24 hours. The dog's mean blood pressure consistently remained above 200 mm. Hg for 5 months after this study, when it was given 1.0 gm. thiosemicarbazide by mouth and died of convulsions.

is not lowered or raised, 2) renal plasma flow increases relatively more than peripheral blood flow, 3) blood flow through other areas does not change, 4) blood viscosity and volume are not altered, and 5) there are no toxic manifestations. Hydralazine does not fulfill all of these criteria, and also causes late toxicity and some unpleasant side effects. However, it is probably the closest approximation available at the present time, the others either being in

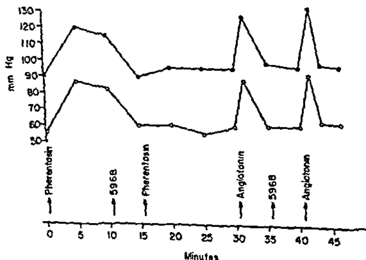


Fig 16 ... of ph... into a... At 10... intrav... subseq... injection of 2 0 units of pherentasin caused little re- ... pressure. A sponse; however, 1 0 unit of angiotonin was pressor. At 35 minutes 5 0 mg of 5968 was injected, the response to another unit of angiotonin 5 minutes later was not inhibited. (From Perry, H. M., Jr., and Schroeder, H. A.: *Am. J. M. Sc*, *228*:396, 1954.)

TABLE XIX

ADRENERGIC BLOCKADE OF VASOACTIVE PEPTIDES (RABBIT AORTIC STRIP)

Blocking Agent	*Pherentasin*	*Hypertensin**	*Serotonin*	*Norepinephrine*
Regitine	0	±		
Dihydroergotamine	0	0	+	+
Iproniazid	sl.	sl.		
Cocaine	0	0		
Dibenamine	0	0	+	+
Pyribenzamine	0			
Atropine	0			
Amine oxidase	+	+	+	+
Tyrosinase	0	+	0	+

* *Probably mainly hypertensin I.*

were also tested. None showed the characteristic alterations of pherentasin activity exhibited by primary amines (Table XIX). Pherentasin was actively inhibited by hydralazine in the intact rat (Fig. 16).

Renin and Angiotonin: On the isolated smooth muscle system, hydralazine in fairly high doses is antagonistic to angiotonin. In the intact animal, this antagonism is not demonstrated by doses sufficient to inactivate pherentasin. A number of antihypertensive metal binding agents, however, inactivate angiotonin in the isolated system, suggesting that a metal is essential for its activity.

Others: Hydralazine inactivates sustained pressor principle, as does β-mercaptopropionate. It also inactivates pitressin.

CLINICAL IMPLICATIONS

A true antihypertensive drug is one which lowers elevated blood pressure to normal without affecting normal blood pressure, in the process of which 1) cardiac output

is not lowered or raised, 2) renal plasma flow increases relatively more than peripheral blood flow, 3) blood flow through other areas does not change, 4) blood viscosity and volume are not altered, and 5) there are no toxic manifestations. Hydralazine does not fulfill all of these criteria, and also causes late toxicity and some unpleasant side effects. However, it is probably the closest approximation available at the present time, the others either being in

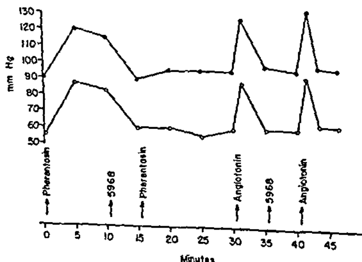


FIG 16 At 0 minutes, after a control period of 20 minutes, 1.0 unit of pherentasin previously found active was injected intravenously into a rat, with the response of systolic and diastolic pressure shown. At 10 minutes 1.0 mg. of hydralazine (apresoline, 5968) was injected intravenously, resulting in an immediate fall of blood pressure. A subsequent injection of 2 0 units of pherentasin caused little response, however, 1 0 unit of angiotonin was pressor. At 35 minutes 5 0 mg of 5968 was injected, the response to another unit of angiotonin 5 minutes later was not inhibited. (From Perry, H. M., Jr., and Schroeder, H. A . *Am. J. M. Sc.*, 228 396, 1954.)

experimental stages, or showing excessive toxicities or only transient effects.

Toxic effects appearing late are those of the development of a syndrome indistinguishable from disseminated lupus erythematosus, reversible when the agent is omitted (93, 184-187). This syndrome has been characterized by: 1) normotension; 2) arthralgia or arthritis, and 3) appearance of elevated cephalin-cholesterol flocculation and thymol turbidity of serum. Continuation of the drug causes later manifestations which include anemia, leukopenia, splenomegaly, hepatomegaly, low plasma cholesterol, albuminuria, microscopic hematuria, azotemia, pleuritis, pulmonary lesions and the appearance of a positive "L-E" test on peripheral blood. These dire events appear only when the drug is continued at full doses. The many bizarre findings of "collagen diseases" can occur. The syndrome has a seasonal incidence, appearing mainly in warm weather. Coming on only after 5 months or more of administration of drug, it is similar to late toxicity from several other metal-binding agents.

Since hydralazine is the only known drug which will produce disseminated lupus erythematosus in man and the dog (188), speculation as to its mode of action may help understanding of collagen diseases. For some time we were attracted to the hypothesis that this syndrome, and perhaps disseminated lupus itself, represented a state of depletion from the body of some material important in the health of ground substance. Loss of a trace metal, or imbalance between essential and abnormal trace metals was considered, in view of hydralazine's known reactions. Feeding of several trace metals failed to influence the disease. The universal appearance of normotension or hypotension before symptoms appeared was in line with this hypothesis. On the other hand, definite hypersensitivity has been observed;

fever, acute arthritis and prostration have occurred within a few hours of giving the drug or its analogues (185,189), both to patients recovering from "hydralazine disease" and to others never receiving the drug before. We have seen showers of L-E cells appear in one recovered person who had taken no drug for 2 years and was given small doses. In several other individuals, reduction of doses has resulted in reversal of symptoms, but not of all laboratory abnormalities. If the L-E phenomenon is one of hypersensitivity, which is not known, this explanation for the disease is tenable. The question is open, but we suspect that its answer will be fruitful of information on hypersensitivity, collagen disease and hypertension.

We do not know which substance is removed from the body by hydralazine or which enzyme system or group of systems is inactivated. The ability to produce this syndrome in man by a drug, however, suggests that lupus erythematosus itself is an enzymatic disturbance which might be affected by replacement therapy. A suggestion of what has been removed in the way of metals may be obtained from trace metal analysis of human urine when hydralazine was given and from cases of known hydralazine disease and known lupus erythematosus (Table XX). The abnormal urines are somewhat low in manganese, somewhat high in tin and zinc. While these findings may not be pertinent to pathogenesis, they deserve study. Blood copper levels were not reduced in this syndrome.

Of the other known functions of hydralazine, carbonyl binding is the most logical to explain the toxicity. It is difficult, however, to conceive of carbonyl binding as leading to depletion. There was no diminution in total carbonyl or pyruvate in blood of patients treated with hydralazine Its other function, removal of sulfhydryl, is also a possible but not probable cause of "hydralazine

TABLE XX

URINARY TRACE METAL CONCENTRATIONS* IN DISSEMINATED LUPUS ERYTHEMATOSUS (111)

	Ti	*V*	*Cr*	*Mn*	*Ni*	*Zn*	*Mo*	*As*	*Cd*	*Pb*	*Sn*	*Comments*
Ch.	<0.05	0.6	5.2	Interf†	1.8	Inter	>50	0.36	1.4	120	38	Lupus
Ev.	<0.05	—	—	<5	5.7	180	21	0.29	1.8	15	5.0	Lupus
Sc.	4.0	0.41	0.36	<5	Inter	175	4.4	0.46	3.0	1.1	3.0	Lupus
Mean**	1.37	0.5	2.78	<5	3.75	177.5	25.1	0.37	2.07	45.4	15.3	
Dr	10	4.9	0.50	<5	2.0	175	6.1	0.58	6.0	170	6.8	Lupus
Ha.	3.6	1.3	1.9	<5	1.4	87.5	12	0.33	<0.3	5.3	17	Lupus
Mean	6.8	3.1	1.2	<5	1.7	131.3	9.0	0.46	3.15	87.65	11.9	
St.	2.8	1.5	0.34	<5	1.1	159	2.4	2.0	70	0.90	8.8	Hydralazine Disease
Sa.	<0.05	0.11	12	<5	4.4	108	3.9	1.2	0.3	0.50	7.8	Hydralazine Disease
Mean	1.43	0.81	6.17	<5	2.75	133.5	3.1	1.6	35.2	0.70	8.3	
Normal												
Mean	<3.8	<0.63	<0.64	<9.7	<2.8	<67	<14	0.80	<0.86	<5.7	<3.2	
Max.	11	2.2	1.0	37	12	135	29	1.4	4	28	5.6	
Min	<0.05	<0.5	<0.05	<5	<0.05	<5	<0.5	0.23	<0.5	<0.05	<0.5	

*Results are expressed in parts per billion
**Specimens supplied by Dr A C Corcoran.
†Interference

disease." Its known antihistaminase activity and the relation of histamine to hypersensitivity is another possible explanation, as is its affinity for pyridoxal.

Lest the reader refrain from using this potent agent when it is needed for the prolongation of life, we can say that hydralazine disease occurs in less than 10 per cent of patients and then only when relatively large doses are given; that it is readily detectable, easily reversible and does no permanent harm if the drug is discontinued in time. There has been no mortality except in unwatched patients, and the drug on the whole is hardly more toxic than many in continuous use for the control of chronic diseases. The method of use is discussed in Chapter VIII.

Chapter V

FACTORS INFLUENCING THE CONVERSION OF NEUROGENIC TO NEPHROGENIC HYPERTENSION

THE TRANSITION FROM INTERMITTENT TO PERMANENT VASOSPASM

If the vasospasm resulting from emotional reactions to stress were confined to the reversible phenomena seen in hyperreactors to pain, the net effects upon the cardiovascular system would be less important than those resulting from exercise. (Unfortunately, at some stage *permanent vasospasm*, at first of slight degree, then more and more pronounced, gradually develops, engrafted upon which are the repetitive reversible episodes of neurogenic vasospasm) The key to the understanding of the pathogenesis lies in this change of reversible to irreversible vasospasm; therefore we may be allowed to theorize for purposes of orientation. The curve of incidence of chronic hypertension in the general population plotted against age (showing a rapid increase in the fifth decade) is consistent with several theories. Since all biologic phenomena can eventually be resolved in terms of physics and chemistry, we should examine possible basic disturbances in that light. The physical explanation—organically induced increase in vascular resistance from sclerosis of all vessels—does not fit the facts, although the effects of increased intra-arterial tension, which both cause cardiac overwork

and which increase the rate of development of atherosclerosis, are beginning to be appreciated. Of chemical explanations we look for some disturbance of some enzyme system concerned a) in the relaxation of smooth muscle, b) the destruction of potential pressor substances, c) the reactivity of blood vessels, or d) the metabolism of the kidney.

THEORY OF HABITUAL REPETITIVE STIMULI

One idea is that the trigger mechanism for emotional discharge to vasospasm becomes more sensitive as the years pass, lesser and lesser stimuli setting off the response. In ✓other words, an habitual pattern of reaction is set up which becomes more and more active and eventually leads to organic renal vascular disease, thereby causing organic renal ischemia. This explanation begs the question and is inconsistent with the fact that demonstrable renal vascular disease may be *absent* in sustained hypertension.

THEORY OF DEPLETION OF VASCULAR SUBSTANCES

Another theory is concerned with the depletion of substances or the wearing out of the mechanisms which cause reversal of vasospasm, i.e., the relaxation of smooth muscle. In other words, repetitive stresses accelerate the aging process in smooth muscle, making it more reactive. There is no evidence for this theory, although as Szent-Gyorgi has pointed out (190), contraction of muscle involves loss of potential energy, relaxation a build-up of energy (phosphate) in the contractile elements. Therefore, slight loss of some substance promoting the restoration of the energy for relaxation may occur with time, or possibly, inhibition of the mechanisms of energy storage by accumulation of another substance. In that event, permanent vasospasm

would result from normally circulating vasoactive substances. This idea has no present basis of fact, although the ions *calcium, magnesium, sodium* and *potassium* are intimately concerned in muscular contraction and relaxation and it is not impossible to believe that imbalances occur with age.

The irritability of muscle, and presumably smooth muscle, depends upon the ratio in extracellular fluids:

$$\frac{Na^{+} + K^{+} + OH^{-}}{Ca^{++} + Mg^{++} + H^{+}}$$

When the concentration in the numerator is increased, irritability increases; when that in the denominator is increased, irritability decreases. The extracellular concentrations, under most conditions, can affect intracellular ones. Therefore, vascular smooth muscle may become more irritable, and therefore contract more, either with higher sodium and potassium levels, by interference or displacement of calcium or magnesium by another inactive element or by their depletion (192).

INTRARENAL ENZYMATIC MECHANISMS

If all nephrogenic hypertension (except azotemic) is dependent upon the same renal enzymatic alterations, it is well to consider and search for reasons as to how this can come about. Hypertension has been produced experimentally in animals, and resulted in man, from a variety of methods of damaging the kidney; most of them can be considered as producing ischemia. Hypertension has also been produced in dogs with no kidneys, kept alive by hemodialysis; whether the mechanism is the same or not is unknown. Yet in man with permanent hypertension there

may be no vascular lesions, no organic renal disease, no organic renal ischemia, but functional changes are found which are obviously dependent upon circulating vasoconstrictor substances provoking spasm. In the dog, spasm is even present distal to renal arterial constriction (10). What is the reason?

To find the answer, we must delve deeper into those mechanisms affected by ischemia in order to think of similar ones altered in the functional state. Something has happened to the kidneys of patients with sustained "functional" hypertension which may be similarly affected in organic renal ischemia We look to altered enzymatic mechanisms to supply us with a common denominator. Because ischemia is related to oxygen tension and oxygen consumption, oxidative mechanisms are the first to be considered Is it possible, therefore, that some renal oxidative enzyme in man is reduced in function by both organic ischemia and an exogenous accumulating substance? If this were so, a population might be exposed uniformly to this substance, but only certain members predisposed to hypertension, i.e , those who react to stress by vasospasm, might develop permanent disease.

Pickering put forth this same idea, that a whole population was "contaminated" but only certain persons developed the disease (Chapter II). This theory is the only one consistent with the known facts and which explains the virtual absence of the disease in many areas of the world For it is likely that a proportion of all human beings react to stress by neurogenic discharges through the sympathetic nervous system.

There are two possibilities, intimately related, which should be explored in order to discover this basic disturbance. Both could explain this most important factor. One involves vitamin B_6, one trace metals.

Theory of Local Vitamin B$_6$ Deficiency: Vitamin B$_6$ is a most prevalent coenzyme, causing reactions described before which are essential for life and health. Deficiency disease in man has been produced by desoxypyridoxine, a metabolic antagonist which may not compete with all the known functions of the vitamin; the principal lesions were of the skin and included cheilosis, chemosis, papular eruptions and dandruff (191) similar to deficiency of other B vitamins or to zinc deficiency (181). Peripheral neuritis has also been produced by isoniazid which causes excretion of this vitamin. In monkeys, loss of hair, weakness, weight loss, muscular wasting, microcytic anemia and skin lesions occur. Obviously we cannot look to generalized vitamin B$_6$ deficiency for explaining human hypertension, nor any other disease, since most patients lack symptoms „and appear in the best of health. In young rats, however, hypertension has been produced by desoxypyridoxine (193-195). Since this coenzyme takes part in all amino acid metabolism, it is possible that a relative or marginal deficiency occurs in the tissues (or kidneys) of populations subject to hypertension; being a local deficiency, generalized lesions would not occur."

Is there a deficiency of vitamin B$_6$ in the American diet? Authorities differ in their opinions. The need for vitamin B$_6$ in man has been established, but the daily requirement has not, being estimated as more than 1.0 and less than 5.0 mg. (191). The vitamin is heat-labile (196) and destroyed by light (197). It is destroyed or removed during the processing of foods, which includes canning and cooking (198, 199). Simple methods for its estimation, depending upon the growth of certain bacteria or yeasts, are considered as giving values too low (200) or too high (201), compared to rat growth curves. The answer is difficult to find.

The American diet, composed as it is of many canned

and processed foods, may be marginal with respect to

pregnant women appear to be somewhat deficient, the growing fetus apparently removing the vitamin from the mother, without causing skin lesions (203-205). Army combat rations were found deficient for monkeys and rats (206, 207), and a brand of infant food was found deficient, causing convulsions (208, 209).

As we have said, there is obviously no generalized deficiency state which can be recognized in the American adult population. Marginal intakes, however, are possible, especially during seasons of the year when the diet is composed largely of processed foods. Converting the values in foods described in the literature to include a daily diet, we have found that the intake is barely adequate (202). About 0.2 mg. per 100 Gm. of food is necessary to promote the growth of rats. Not many foods contain this much when cooked and it was difficult to calculate a 2.0 mg. intake in a sample hospital diet (202).

Why do not pronounced deficiency symptoms appear? Apparently this coenzyme has an affinity for systems where it is most needed for life and less for health. Its distribution in organs shows wide variations (201). Perhaps renal deficiency can exist without deficiencies elsewhere; perhaps overloading of one vitamin B_6 enzyme system by metabolic products can produce a state of local deficiency without it being manifest in other systems. The need for a coenzyme varies as the load placed upon the enzyme system, as is so well known in the case of vitamin B_1 or thiamin. A third possibility is that specific antagonists accumulate with age.

Trace Metal Imbalance: The second theory concerns metalloenzymes. There are many in the kidney. If deficiency of a metal were produced, that enzyme would be-

TABLE XXI

URINARY EXCRETION OF TRACE METALS IN NORMOTENSIVE AND HYPERTENSIVE STATES (γ/L.) (111)

		Mn	*Zn*	*Mo*	*V*	*Cd*	*Ti*	*Pb*	*Cr*	*Ni*	*Sn*	*Ag*
(ormotensive .5 cases	Mean	<9 7	66 8	14 0	<0 6	<1 1	<3 75	5.7	<0 64	<2 78	<3.22	0.80
	Range	< <5–37	<5–135	<0 5–45	<0 3–7 5	<0 5–4	<0 05–10.7	<0 05–28	<0 05–1.0	<0.05–12	<0.5–10 25	0.4–1.4
Untreated hypertensive 16 cases	Mean	54 11	106 3	10.63	1 95	37 0	5.83	14 23	0.88	5 53	8 93	1 21
	Range	<5–305	31–355	2 1–26	<0 2–14 5	<0 5–370	<0 5–31	0 93–50	<0 05–4.4	<0.1–16.8	0 5–41	0 3–4.6
Untreated hypertensive 8 cases	Mean	62 6	109 7	7.59	2 86	41.7	3 21	10 3	0 67	3.99	5.47	1.44
	Range	<5–305	5–205	3 8–15 5	0 4–14 5	<0 5–370	1.8–5 3	0 06–50	<0 05–3 1	1 1–6.75	0 5–10 5	0.3–4.6
Same treated*	Mean	12 14	89 75	4 54	0 93	3 14	3 97	2.19	0.71	5.78	2.64	0.73
	Range	<5–36	31–170	0 5–10 25	0 27–1 85	<0 5–18	0.8–11	< <0 5–4.9	<0 05–2.6	0.3–28.5	0.3–9	0.24–1.7
Hydralazine disease 2 cases	Range	<5	108–159	2 4–3 9	0 11–1 5	0 5–70	<0 05–1.8	0 5–0 9	0.34–12	1.1–4 4	7.8–8.8	1.2–2.0
Disseminated lupus 5 cases	Mean	<5	154	18 7	1 80	2.5	3 54	123 5	1.99	2.7	13.96	0.40
	Range	<5	87 5–180	4.4–>50	0 5–4 9	0 3–6 0	<0 05–10	1.1–170	0 4–2.8	1.4–5.7	3.0–38	0 29–0.5

* By ganglionic blockade and Hydralazine
From data of Perry and Schroeder.

come inactive until the metal were replaced. There is no evidence at the present time that specific metal deficiencies exist in man, with the possible exception of zinc in undernutrition. On the contrary, there are many trace metals in American tissues which perhaps are not only unnecessary but undesirable. The kidney is notable in this respect (Chapter VI).

(Because an undesirable metal can replace an essential one in an enzyme system and inactivate it *in vitro*, it is probable that such a consequence can occur *in vivo*) In order to determine where to look, we must examine the essential and the presumably abnormal trace metals in American human adult tissues and urine (Table XXI), compare them with metals found in infants to discover which accumulate with age, and also compare the tissue content of people from areas not exposed to hypertension. This subject will be discussed in Chapter VI, but examples can be considered here.

C[illegible]

ca[illegible]

An examination of the inhibitory effects of a number of trace metals upon DOPA decarboxylase and monamine oxidase revealed the following: Some inhibition was exhibited by all in high concentrations, but at low (0.1 millimolar), only cadmium and mercury significantly inhibited enzymatic activity of DOPA decarboxylase; both inhibited monamine oxidase to less extent (Table XXIII). Both are nephrotoxic and will displace zinc (p. 146).

(Any disease which is a function of aging may be influenced by the gradual accumulation in tissues of those trace metals which appear to show organ selectivity and poor excretion.) Any diseases appearing frequently as a function of Western Civilization which are virtually absent in uncivilized man may be influenced by accumula-

TABLE XXII
Change in Several Metals with Age (P.P.M. Ash)*

Decade	No Cases	Kidney						Lung		Liver					
		Ni	Zn	Cd	ΔZn-Cd	Pb	Sn	Al	Ti	Ti	Ni	Cd	Sn	Cr	Pb
0	5	6†	1850	0	1850	13	15‡	77	0	0	0†	0	3‡	22	34
1	2	0	2050	160	1890	36	134	60	0	0	0	0	103	15	45
2	1	10	4700	1450	3250	68	33	440	82	14	0	190	66	21	115
3	4	14 5	5800	2750	3070	130	17	>1540	220	7	12	174	38	16	171
4	3	10	5100	2500	2600	115	37	>2400	>740	19	<33	167	124	16	140
5	5	13	6300	3500	2800	96	91	>>2320	>660	22	0	186	33	14	77
6	6	16	7450	4200	3200	96	24	>>2660	>910	10	<4	282	27	35	115
7+	4	51	6050	2850	3200	71	44	>>3000	>900	10	37	385	36	17	77

* After Tipton (231)

† Present in only 1 stillborn Present in 7-week-old child only.

‡ Absent to trace in stillborn Present in 7-week-old child only. These values are indicative of concentration in wet weight of organ ±10%. The remarkable constancy of the differences between zinc and cadmium suggests that as cadmium is accumulated, displacing zinc from enzymes, more zinc enzymes are formed. If they were not, this amount of cadmium would cause overt renal toxicity.

tion of those abnormal trace metals to which civilized man is exposed. Cardiovascular diseases associated with aging therefore may be influenced by accumulation of trace metals in kidney, liver, blood vessels, adrenal or brain.

In Table XXII are shown evidences of accumulation of various trace metals or lack of it in American kidneys with age. Although the numbers in each decade are small, the trends are definite for nickel, titanium and cadmium, not so for tin. Zinc is accumulated in proportion to cadmium. One of these metals could be the culprit, although we suspect cadmium because of its prevalence (see p. 146).

Other oxidative metalloenzymes in kidney (or elsewhere) might be affected by abnormal exogenous trace metals. Two pertaining to the problem of hypertension are listed in Table XXIII. (Any enzyme containing free sulfhydryl groups can be inactivated by metal binding thereon; thus, metalloenzymes are not essential for inactivation by metals.) Direct evidence for their participation is lacking, but they are shown to call attention to their role in nitrogen metabolism, direct or indirect, and to their metalloenzyme natures Vanadium and cadmium have striking actions.

Theory of Electrolyte Imbalance: Small elevations in the serum sodium of hypertensive patients have been reported from time to time (210, 211). Their significance is unclear The hypertensive kidney is a salt-losing kidney; no functional or morphological alterations in adrenal cortex have been demonstrated in the usual case. There is evidence, however, that the sodium content of arterial walls may be increased, causing enough swelling to increase peripheral resistance (212). There is also evidence that the sodium in the body affects vascular irritability in that the peripheral vessels become less sensitive in sodium depletion and more sensitive in sodium repletion and the administration of desoxycorticosterone ace-

TABLE XXIII

EFFECT OF METAL IONS ON TWO ENZYME SYSTEMS (GUINEA PIG) (% ACTIVITY) (311)

Metal	Bound by Hydralazine	DOPA Decarboxylase Millimolarity of Metal ion				Monamine Oxidase (Substrate, tryptamine) Millimolarity of Metal ion			
		10	1	0.1	0.01	10	1	0.1	0.01
Mg^{++}		103	—	—	—	94	99	99	96
Ti^{+++}		24	82	94	98	87	101	106	103
Ti^{++++}		52	92	103	98	100	100	101	99
V^{+++}	+	11	99	113	97	185	137	118	110
V^{++++}		7	100	99	94	256	154	104	108
V^{+++++}	+	96	—	—	—	127	106	101	99
Cr^{+++}*		34	100	—	—	90	102	102	104
Cr^{+++}	0	26	77	86	92	110	111	96	106
Mn^{++}*	+	84	94	—	—	98	91	98	94
Fe^{++}	+	70	100	—	—	106	103	101	102
Fe^{+++}	+	32	106	105	—	106	104	98	103
Co^{++}*	0	69	91	94	94	144	136	109	107
Ni^{++}*	+	33	100	—	—	110	107	102	105
Cu^{+}		60	93	—	—	58	114	101	96
Cu^{++}	+	8	13	91	93	18	110	86	101
Zn^{++}	0	41	83	93	93	93	—	—	—
Cd^{++}	0	2	9	54	89	86	82	88	94
Hg^{++}	+	—	6	58	86 (89)	1	64	102	106
UO_2^{--}		93	105	99	101	127	98	100	97
$Me^{++}Na_2EDTA$									
$Mg^{++}Na_2EDTA$		104	110	—	—	127	116	102	92
Ca^{++} "		103	101	—	—	108	102	106	91
Mn^{++} "		106	107	—	—	126	109	107	103
Fe^{++} "		100	105	—	—	—	117	107	—
Na_2 "		95	94	—	—	125	118	115	101
Na_2 " (24 hr.)		102	—	—	—	—	—	—	—

Italicized figures represent 20% change Note the specific effects of Cd, Hg, V, Co (*cf.* Table XIII, p. 88). Those in parenthesis show dilutions by 10

* Depressor in hypertensive rats as EDTA complex. (Figs. 13 and 14, pp. 105-107.)

tate. What change affecting sodium intake, loss or shift occurs in hypertension is not known. There is no correlation with salt intake in man, although moderately hypertensive rats choose to eat more. The alteration must be an esoteric one, and may involve potassium and magnesium or possibly calcium as well.

Theory of Mechanical Renal Arterial Obstruction: In view of the above discussion, it is highly possible that enzymatic alterations secondary to organic ischemia and those caused by one or more of the aforementionel factors may be similar. If so, partial obstruction of a renal artery by atherosclerotic plaques could provide the necessary mechanism for permanent hypertension just as well as could intrarenal enzymatic changes from trace metals or coenzyme deficiency. Such obstructive lesions exist and may be more common than realized (145). One can imagine a hypothetical case· a man with the ability to react to stress by vasospasm passes through his first five decades only with tachycardia or transient hypertension under the stimulus of an examination. In his fifth decade in our civilization, he begins to develop overt atherosclerosis, plaques of which are deposited by chance or by dynamic design at the mouths of his renal arteries. He then develops hypertension, caused by some organic renal ischemia and some neurogenic vasospasm. As the hypertension increases the rate of development of atherosclerosis, these plaques may become larger, leading to further renal ischemia and hypertension but without much intrarenal arterial sclerosis He dies in his sixth or seventh decade, usually of an atherosclerotic complication. This sequence of events may be very common and does not necessitate trace metal imbalance or other enzymatic disturbance, unless a common disturbance influences both hypertension and atherosclerosis (Chapter VII). Further-

TABLE XXIII

EFFECT OF METAL IONS ON TWO ENZYME SYSTEMS (GUINEA PIG) (% ACTIVITY) (311)

Metal	Bound by Hydralazine	DOPA Decarboxylase Millimolarity of Metal ion				Monamine Oxidase (Substrate, tryptamine) Millimolarity of Metal ion			
		10	*1*	*0.1*	*0.01*	*10*	*1*	*0.1*	*0.01*
Mg^{++}									
Ti^{+++}		103	—	—	—	94	99	99	96
Ti^{++++}		*24*	*82*	94	98	87	101	106	103
V^{+++}		*52*	92	103	98	100	100	101	99
V^{++++}	+	*11*	99	113	97	*185*	*137*	118	110
V^{+++++}		*7*	100	99	94	*256*	*154*	104	108
Cr^{++}*	+	96	—	—	—	*127*	106	101	99
Cr^{+++}		*34*	100	—	—	90	102	102	104
Mn^{++}*	0	*26*	*77*	86	92	110	111	96	106
Fe^{++}	+	84	94	—	—	98	91	98	94
Fe^{+++}	+	*70*	100	—	—	106	103	101	102
Co^{++}*	+	*32*	106	105	—	106	104	98	103
Ni^{++}*	0	*69*	91	94	94	*144*	*136*	109	107
Cu^{+}	+	*33*	100	—	—	110	107	102	105
Cu^{++}		*60*	93	—	—	58	114	101	96
Zn^{++}	+	*8*	*13*	91	93	*18*	110	86	101
Cd^{++}	0	*41*	83	93	93	93	—	—	—
Hg^{++}	0	*2*	*9*	*54*	89	86	82	88	94
UO_2^{--}	+	—	*6*	*58*	86 (89)	*1*	*64*	102	106
$Me^{++}Na_2EDTA$		93	105	99	101	*127*	98	100	97
$Mg^{++}Na_2EDTA$									
Ca^{++} "		104	110	—	—	*127*	*116*	102	92
Mn^{++} "		103	101	—	—	108	102	106	91
Fe^{++} "		106	107	—	—	*126*	109	107	103
Na_2 "		100	105	—	—	—	117	107	—
Na_2 "		95	94	—	—	*125*	*118*	115	101
(24 hr.)		102	—	—	—	—	—	—	—

Italicized figures represent 20% change. Note the specific effects of Cd, Hg, V, Co (*cf.* Table XIII, p. 88). Those in parenthesis show dilutions by 10.

* Depressor in hypertensive rats as EDTA complex. (Figs. 13 and 14, pp. 105-107.)

guish between these conditions and functional neurogenic vasospasm; they can be presumed to react in the same way. Therefore, in late stages, arteriolar nephrosclerosis, caused by the hypertension, produces organic renal ischemia which sustains the hypertension. As discussed previously, we probably cannot use this mechanism to account for middle stages of sustained hypertension, because organic lesions are often not present.

Similarly, the tubular part of the nephron may be unable to distinguish the difference between organic arterial and arteriolar narrowing from these causes or from intrarenal arterial obstruction by scars (pyelonephritis), and glomerular obstruction (nephritis and glomerulosclerosis). The locus of the mechanism reacting to renal ischemia may be postglomerular (tubular), or it may be in the juxtaglomerular apparatus which lies around the afferent arteriole. In the latter case, chronic glomerulonephritis might not be expected to cause hypertension until fairly widespread renal degeneration had occurred. This may be the usual situation.

Comment: One can only guess at which factor operates in a given hypertensive patient. There may be several others not mentioned. The theory of vicious cycles or cybernetics is quite prominent in much of what has been said, as it is in many pathologic states and normal metabolic pathways (which are far from vicious until disturbed). This mechanism, which transforms intermittent neurogenic vasospasm into permanent nephrogenic and neurogenic hypertension, is the "killer." Therefore, it becomes of foremost importance to understand it for treatment. If we could counteract this one mechanism and break the cycle, perhaps hypertension would be a mild, relatively nonfatal, but interesting physiologic abnormality.

more, cholesterol emboli in the kidneys have occurred from plaques (213), associated with hypertension.

The renal hemodynamic picture of hypertension in older persons is that of the major resistance being on the arterial side of the glomerulus (214), contrary to that seen in younger people where it is predominantly in the efferent arterioles. If the disease begins in the 50's and 60's, such sequential events are likely pathogenetic features, although it is now impossible more than to guess which comes first. A vicious cycle of this sort involves the initiation of nephrogenic hypertension by local atherosclerosis and the progression of atherosclerosis by hypertension, with the predisposing factor (neurogenic vasospasm) present, however, for the previous lifetime of the individual.

Sustained chronic hypertension causes arteriolar nephrosclerosis, characterized in order of appearance, by: 1) thickening of the glomerular capsule; 2) thickening of the glomerular intercapillary substance; 3) thickening and hypertrophy of the walls of the arterioles; 4) intimal thickening, and 5) fibrosis and hyalin degeneration of the walls of arterioles and small arteries. In neurogenic hypertensive dogs, these alterations take 2 to 4 years to develop (7); in man with chronic hypertension, little or no changes are apparent in half of biopsies (159) while almost all show it at necropsy (2). When pheochromocytomata act as the neurogenic factor for long enough, arteriolar nephrosclerosis is the frequent result, and nephrogenic hypertension may remain after removal of the tumor.

When arteries and arterioles are narrowed by permanent sclerotic changes, blood flow to nephrons is obviously reduced at normal blood pressure levels. It matters little to a nephron whether its flow is cut down by a single aortic and renal arterial plaque or by organic narrowing of its afferent blood vessel. Perhaps its tubules cannot distin-

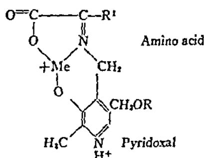
TABLE XXIV

VARIOUS EFFECTS OF PYRIDOXINE IN MAN WITH ESPECIAL REFERENCE TO ANTAGONISM TO METAL-BINDING AGENTS

Clinical Finding	*Induced by Metal-binding Drug*	*Relieved by Vitamin B_6*	*No Reports*	*Remarks*
Convulsions	Isoniazid	Yes	1	
Convulsions	Semicarbazide	Yes	1	
Peripheral Neuritis	Isoniazid	Partly	1	Local disorder
Leukopenia and agranulocytosis	Thiouracil	Yes	5	
	Sulfonamides	Yes	2	
Peripheral Neuritis	Arsenic	Yes	1	
Cheilosis, Chemosis, etc.	EDTA	No	1	Zinc deficiency
Same	Desoxypyridoxine	Yes	2	
Same	Spontaneous	Yes	8	
Seborrhaeic Dermatitis	Desoxypyridoxine	Yes	2	
Same	Spontaneous	Yes	4	Applied locally

Vitamin B_6 Selected Annotated Bibliography, 1954. Merck & Co.

Can we bring some of these ideas together into one theory? In the case of enzymatic mechanisms, we can. For pyridoxal phosphate is believed to contain a metal necessary for activity, chelated to the pyridoxal-amino acid complex in the following manner (215):



We have demonstrated that cadmium and mercury can selectively inhibit at least one pyridoxal enzyme, probably by competing with the essential metal, just as a number of strong metal binding agents also inhibit this same enzyme (Chapter IV), probably by removing the essential metal. Therefore, certain trace metals can be biochemically interrelated with certain pyridoxal enzymes. It is possible that not only the decarboxylases, which produce the vasoactive and cerebroactive primary amines serotonin, tryptamine, tyramine, isoamylamine, dihydroxyphenylethylamine from amino acids, but also transaminases may be inhibited by abnormal trace metals (Table XXIV).

CLINICAL IMPLICATIONS

The existence of organic narrowing of renal arteries and arterioles must be in mind during every attempt to reverse or control hypertension, whether by drugs or surgery. No available therapeutic measure known will dilate renal arteries and arterioles more than they can dilate through smooth muscular relaxation; scar tissue will not

mechanisms are unknown but the clinical and laboratory evidence that adrenal steroids cause hypertension in certain cases is clear. The reader should remember, however, that there is no evidence that the adrenal cortex is overactive in most cases of neurogenic or nephrogenic hypertension, but that isolated instances in which it plays a definite and perhaps primary role are known.

Experimental Steroid Hypertension: For many years it has been recognized that desoxycorticosterone (DOCA), a salt retaining hormone, will cause hypertension in rats when added salt is given (216, 217). Likewise, a syndrome similar to toxemia of pregnancy can also be produced, relieved or prevented by hydralazine (218). Feeding of salt alone in excessive quantities can produce rat hypertension (219); vascular lesions result. The amount of steroid and the amount of salt necessary to produce this disorder are far beyond physiologic limits. DOCA is pressor in renal hypertensive dogs (220) and hypertensive patients (221). Salt restriction apparently induces adrenal cortical hyperactivity (222).

Effect of Experimental Nephrogenic Hypertension on Adrenals: Adrenal hypertrophy accompanies experimental nephrogenic hypertension (223). Furthermore, rats with moderate hypertension voluntarily drink more saline than do normals or their paired severely hypertensive mates (224). This increased requirement for salt may be a reflection of the salt-losing tendencies of ischemic kidneys, already discussed in Chapter IV.

Relation of Adrenal Cortex to Medulla: It may not be a coincidence that the adrenal medulla, concerned with the release of epinephrine, and the cortex, concerned with sugar, salt and sex, are enclosed in the same gland. There is an intimate relationship between the two hormones acting on vascular smooth muscle. There may be a further,

become more elastic. This statement may not hold true, however, for cholesterol-filled atheromata, which probably can be partly absorbed under the proper conditions.

Fortunately, the cases of severe hypertension which become azotemic when the blood pressure is lowered are rare. When present, azotemia may be worsened. The existence of renal arterial constriction can make therapy difficult; however, intrarenal constriction beyond the obstruction probably can be quite readily opposed.

The existence of organic narrowing of other major arteries to myocardium and brain must be in mind during every attempt to reverse or control hypertension, for a lowered peripheral pressure may cause ischemia beyond the obstruction. These circumstances are fortunately uncommon.

Because hydralazine and similar compounds appear to attack the factor converting intermittent into permanent vasospasm in time, this drug is indicated in all patients with sustained hypertension who are able to tolerate it without symptoms of sensitivity. Whether or not it helps to restore a disturbed enzyme system to normal function, or merely makes abnormality more abnormal, is not known at this time. Its reactions on DOPA decarboxylase suggest that amino acid decarboxylation would be suppressed by the kidney, thus preventing the formation of amines; its actions on monamine oxidase suggest that it can promote the destruction of amines; its inhibition of pherentasin suggests that it specifically inactivates the one pressor substance found in the hypertensive state.

ADRENOCORTICAL MECHANISMS

One possible factor which may influence the conversion of intermittent to sustained vasospasm lies in the adrenal cortex and in its influence on electrolyte balance. The

readily when deprived of sodium; conductance is restored by a number of quaternary ammonium compounds (229). Whether or not increased conductance occurs when there is an excess of intraneuronal sodium is not known. The decreased sensitivity, and the sometimes lowered blood pressure, seen when dietary salt is severely restricted, may perhaps be explained on this basis.

These interactions between nerve transmission, salt, vasoconstrictor substances and steroids can explain some of the clinical findings which appear on the surface to be inexplicable. Normal vasomotor tone, normal discharges of sympathetic fibres, normal amounts of norepinephrine can produce generalized vasospasm when the vascular smooth muscle becomes hypersensitive through salt and steroids. Removal of salt or steroids may restore sensitivity to normal. Excessive vasomotor tone, excessive discharges of sympathetic fibres, excessive amounts of norepinephrine formed at nerve endings can produce a much greater degree of generalized vasospasm when the vascular smooth muscle becomes hypersensitive. Removal of salt or steroids restores sensitivity to normal but does no more than partly reduce the vasospasm to a lesser level; to achieve strict normality requires additional restoration of sympathetic activity to normal. When the vasospasm is in part caused by circulating humoral pressor substances, restoration to a normal state is impossible unless these substances are inactivated.

Clinical Findings: Many, but not all, patients with adrenal cortical adenomata or hyperplasia have hypertension Other steroid-producing tumors may also be associated with hypertension. Hypertension is uncommon, but not unknown, in virilizing tumors; we have seen it regress on surgical removal of the tumor. Cushing's syndrome is

more basic, relationship between salt-retaining hormone and the transmission of nerve impulses along sympathetic fibres, affected by sodium or potassium.

1. The administration of DOCA increases the sensitivity of vascular smooth muscle to epinephrine and norepinephrine (38).

2. The vessels of the patient with Addison's disease show a relatively low reactivity to injected epinephrine and norepinephrine (225, 226).

3. Salt restriction decreases these sensitivities; salt repletion increases them.

4. The hypertensive, but not the normotensive, individual responds to intravenous DOCA by a rise in blood pressure (221).

There are two possibilities to explain these findings. The first is concerned with the smooth muscle fibre, the second with unmyelinated sympathetic nerve fibres. Certain adrenal cortical steroids apparently act at the cellular level, regulating the amount of sodium, potassium and possibly magnesium within the cell (227, 228). At least there are rather profound alterations in cellular content of cations when salt-retaining hormones are given or are formed in excess; in extracellular fluid there is apt to be hypernatremia, hypokalemia and alkalosis of variable degrees. If smooth muscle cells were so affected, the result might be hyperirritability of the fibres with excessive responses to vasoconstricting impulses, either neurogenic or mediated through circulating pressor substances. Perhaps the intracellular edema found in the arteries of some hypertensive individuals (212) is on this basis.

Another theory involves the effect of sodium or potassium on nerve transmission through unmyelinated fibres. The fibres of primitive animals do not transmit impulses

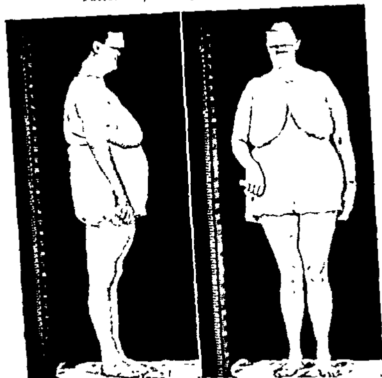


FIG 17 Central obesity, menstrual irregularities, low sweat salt (<20 mEq/L) and hypertension Rapid weight gain, mild hirsutism, easy bruisability and moderate diabetes were also present. This complex has been named the "endocrine hypertensive syndrome" for want of a more definitive word The blood pressure was highly responsive to salt restriction (3, 3c)

They may be recognized by the presence of central obesity and hypertension, in women menstrual irregularities are common (Fig. 17). The condition has been seen in families (3). Presumably their hypertension is influenced by an overproduction of aldosterone or other salt-retaining hormones, which decreases the sodium in sweat to low levels We must hypothecate the chain of events in the

not invariably associated with hypertension; primary aldosteronism, in which there is overproduction of salt-retaining hormone, appears to be.

The administration of [illegible] tropic hormone (ACTH) i[illegible] pertension. In such cases, w[illegible] of vascular smooth muscle increased because of the mild *salt-retaining side effects of these agents, which are not of* themselves primarily concerned with salt. In the presence of a normal or decreased sympathetic tone, cortisone should be inactive in this respect. Hormones with lesser salt-retaining qualities, hydrocortisone, metacortandren, etc., are less active. DOCA, on the other hand, produces hypertension in a fair number of Addisonian patients treated with large amounts of salt.

Therefore, the pressure-raising activities of steroids and salt, according to this theory, are not primary qualities residing in the substances themselves, but depend principally upon the state of the neurogenic control of vasoactivity. If sympathetic tone is elevated, they elevate pressure. If sympathetic tone is low, they do not, *unless* excessive hyperphysiologic amounts are given. Abnormal amounts of any hormone can cause profound derangements which would not occur with physiological replacement.

There is a group of patients, now being better described, which appears clinically to show excessive adrenocortical activity of two or three types of the hormones concerned with salt, sugar and sex. There are many clinical variations from the "normal," extending from minor degrees to the borderline of full-blown Cushing's syndrome. So far, all have had either adrenal cortical adenomata, often small, or pituitary basophilism with adrenal hyperplasia.

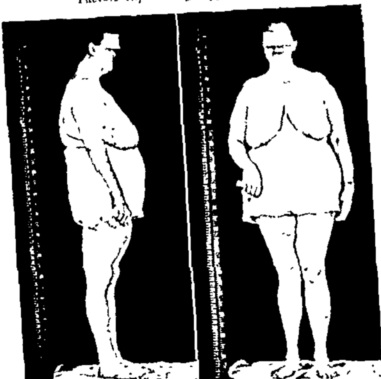


FIG 17 Central obesity, menstrual irregularities, low sweat salt (<20 mEq/L) and hypertension Rapid weight gain, mild hirsutism, easy bruisability and moderate diabetes were also present This complex has been named the "endocrine hypertensive syndrome" for want of a more definitive word The blood pressure was highly responsive to salt restriction (3, 3c)

They may be recognized by the presence of central obesity and hypertension, in women menstrual irregularities are common (Fig 17) The condition has been seen in families (3) Presumably their hypertension is influenced by an overproduction of aldosterone or other salt-retaining hormones, *which decreases the sodium in* sweat to low levels. We must hypothecate the chain of events in the

absence of exact hormonal measurements. A small adenoma forming only aldosterone will produce hypertension, hypokalemia and alkalosis. One forming both aldosterone and hydrocortisone or cortisone-like hormones will produce hypertension and central obesity, with the resultant muscular weakness, thin skin and possibly menstrual abnormalities. One forming both hormones plus androgens will induce in addition hirsutism, an enlarged clitoris, menstrual irregularities, muscular hypertrophy, maleness and the like. There can therefore be seven clinical types, only four of which are associated with aldosterone and hypertension, four with central obesity and four with androgenic overproduction. While the distinctions between cases are not as simple as outlined here, since a single hormone may have the minor side effects of another, this idea is worth considering from clinical grounds and can explain the presence or absence of these different clinical manifestations. In aldosteronism the tumor is probably derived from cells of the zona glomerulosa. The severity of the manifestations naturally depends upon the amounts of hormones produced in excess.

Hypertension and Hyperaldosteronism: Recent studies have shown that there is a mild "hyperaldosteronism" in severe and malignant hypertensive patients as evidenced by the salt-retaining properties of urinary extracts in adrenalectomized rats (230) If this is so, it is possible that vascular hyperreactivity is dependant upon a slight excess of this hormone However, taking into consideration all of the data concerning the adrenal cortex in hypertension, this theory is hardly tenable.

The hypertensive kidney loses salt under a load, and the more severe the hypertension in terms of nephrosclerosis, the greater is the tendency to lose salt. Since salt de-

pletion, or some electrolyte abnormality, may be the stimulus to the formation of aldosterone, it is possible that the mild aldosteronism measured may be merely a reflection of this salt-losing tendency, which probably has its seat in the kidney. Slightly excessive production of aldosterone could be predicted from knowledge of chronic renal salt loss Obviously, this form of adrenal cortical hyperfunction would cause, if a primary initiating factor, salt *retention* by the kidney, a phenomenon opposite to what is actually encountered.

CLINICAL IMPLICATIONS

Obviously, patients with hypertension influenced by adrenal cortical overactivity should respond to restriction of salt by a lowered blood pressure. They do. The fact that severe sa[illegible]
tension secor[illegible]
the role of th[illegible] in this state. Severe salt restriction
[illegible]
[illegible] results do *not mean* that *all* human hypertension is dependant upon steroids and salt; on the contrary, these cases are in a *minority*. The reader must remember the simple fact that dietary salt restriction of severe degree causes overactivity of the adrenal cortex and that the usual hypertensive kidney is a salt-losing kidney to an extent dependant upon the degree of rena damage or renal ischemia

The clinician does well to recognize cases of aldosteron hypertension, for treatment of them may differ radicall from that of the usual case of neurogenic or nephrogeni hypertension. Although eventually arteriolar nephroscl rosis develops, a lesion dependant only on diastolic hype

tension from any cause, it seems slow to occur in these cases and is apt to be less severe than in other types (3, 4). Salt restriction, antiadrenal hormones and adrenalectomy are logical methods to use if diagnosis can be accurate. None of these measures is necessary nor justifiable in other types. Therefore, their recognition becomes of practical significance. The measurements of sodium in sweat (3) or saliva and of specific steroids in urine or blood are specialized diagnostic procedures for such cases.

Chapter VI

TRACE METALS AND CARDIOVASCULAR DISEASE

INTRODUCTION

BECAUSE of the strong suggestion that trace metal imbalances may be involved in some of the chronic diseases to which the people of Western Civilization are exposed, a chapter on this subject is in order. To be considered are the relations of metalloenzymes to the problem, the concentrations of essential trace metals in human tissues, the presence and amount of abnormal metals and from whence they may come, and the possibility of their interference with metalloenzymes to such an extent that they cause chronic diseases. Because this subject represents a new frontier in Medicine, vast gaps in knowledge exist but the pattern is clearing.

By trace metals we will consider only those present in small or relatively minute amounts and not discuss the "bulk" metals, sodium, potassium, magnesium and calcium, nor iron which has an intermediary position between ubiquitous elements and trace metals. All bulk metals probably take part in enzymatic reactions or in exchange mechanisms; trace metals are often confined to more specialized systems If interference with one of the bulk metals occurred in the body, profound toxicity would result. For example, should all magnesium enzymes be inhibited, intermediary metabolism would cease; if calcium were displaced, muscular relaxation would cease. Partial

inhibition of some of these systems undoubtedly occurs in disease, but many can be recognized.

There are many metalloenzymes in mammalian tissues, but only five essential trace metals have been identified: manganese, cobalt, copper, zinc and molybdenum. Deficiency of one of these trace metals in a metalloenzyme, either by depletion or displacement by another more or less active metal can be expected to lead to a profound metabolic disturbance induced in a very basic and discrete level. There is growing evidence that arterial hypertension and possibly atherosclerosis may be influenced by trace metal imbalances induced by exposure to and accumulation of abnormal trace metals resulting from products confined to Western Civilization.

METALS CONCERNED IN METALLOENZYMES

For a metal to be reactive in oxidation-reduction mechanisms, it must contain at least two valence states which are fairly readily transposed. The essential metals, iron, manganese, cobalt and copper, fit the requirement, as do titanium, vanadium, chromium and nickel of the first transitional group. For a metal to chelate* readily, a requirement for enzymatic activity (232), it should usually

* The definition of chelation and complex formation can best be given by quoting from Martell and Calvin (233): "When a metal ion combines with an electron donor, the resulting substance is said to be a complex, or coordination compound. If the substance which combines with the metal contains two or more donor groups so that one or more rings are formed, the resulting structure is said to be a chelate compound, or metal chelate, and the donor is said to be a chelating agent The electron-pair bonds formed between the electron-accepting metal and the electron-donating complexing or chelating agent may be 'essentially ionic' or 'essentially covalent' depending on the metals and donor atoms involved. Without further considering the nature of bonds, simple examples of complex formation and chelation are represented schematically as follows:

have a coordination number of 4 or 6, an index of the number of donors of the chelate with which the metal will combine. Thus, magnesium, aluminum, vanadium, chromic ion, manganous and manganic, ferrous and ferric, cobaltous and cobaltic, nickelous and nickelic, tin and lead have coordination numbers of 6, while zinc, cupric, cadmium, mercury, silver, gold have one of 4 and molybdenum of 8. Those of titanium and scandium have not been determined (233). Some functional groupings which bind metals are carboxyl, hydroxyl, carbonyl, amino (primary, secondary, tertiary, cyclic tertiary), sulfhydryl, thioether, sulfonate and phosphonate (232).

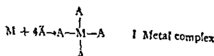
Principles of Chelation: The general rules regulating the stability of metal chelates, according to Bailar (234) are as follows:

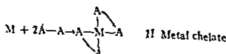
1. Ring structures involving metals and organic con-

... six unhindered rings in its presence are the most stable.

3 Fused rings, that is, configurations in which two or more rings have a common side, have a greatly increased

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where M represents a metal ion, Ä represents a complexing agent; and Ä—Ä represents a chelating agent."

stability, e.g., ethylenediamine tetraacetate (EDTA) is 50 times more stable than predictions would indicate.

4. Maximum stability is achieved in the presence of a minimum charge. Thus inner salts are maximally stable.

5. Spatial factors are important. Thus primary amines are better than secondary amines which in turn are better than tertiary amines, probably because the methyl groups are cumbersome. Similarly water is better than alcohol which in turn is better than ether; methanol is better than ethanol, and n-propanol is better than isopropanol. In addition each internal angle of a five membered ring should approximate 108°. If the ring involves an aromatic nucleus and its resultant obtuse external angle, no chelate is formed.

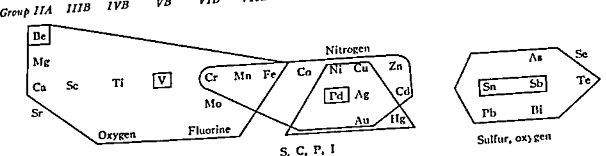
6. The active groups involved in chelation are (1) fluorine and oxygen, (2) nitrogen, (3) sulfur, carbon (CN, carbonyl), phosphorus (as phosphene), and the halogens. The first group has maximum binding capacity for beryllium with a secondary one for vanadium. The second group has a maximum binding for cobalt, and the third for palladium and copper. In addition both sulfur and oxygen bind metals centering around tin and antimony in the Periodic Table (Table XXV).

7. Transition metals are the most strongly bound because their inner shells are unfilled and allow a shifting of electrons to meet the optimum chelating requirements whereas other metals are much more rigid in the way they can accept or donate electrons.

The spatial type of chelate is also of interest (Table XXVI). Beryllium and boron, zinc, cadmium and mercury form tetrahedral complexes. Presumably the first two could resemble magnesium chelates, the last three each other. Copper, silver, gold, and nickel form square complexes, while all of the other essential metals, save molybdenum

TABLE XXV

AFFINITIES OF VARIOUS COMMON TRACE METALS FOR CHELATION BY DIFFERENT ACTIVE GROUPS*



* After Bailar (234).

TABLE XXVI

NORMAL AND ABNORMAL METALS IN CHELATES (233)

Coordination No.	*Tetrahedral*	*Square*	*Octahedral*	*Dodecahedral*
4	Zn^{++}	Cu^{++}		
4	Cd^{++} Hg^{++}	Ag^{++} Au^{+++} Ni^{++}		
6	Mg^{++}			
6	Be^{++} B^{+++}			
6			Mn^{+++} Fe^{++} Co^{++} Co^{+++}	
6			Cr^{+++}	
6			Al^{+++} Pb^{++++} Sn^{++++}	
8				Mo^{++++}
8				W^{++++}

See footnote p.193.

form octahedral ones, as do chromium, aluminum, tin and lead. Thus, possible interfering metals may be roughly grouped according to their chelate forms. Those of the first transitional group have the requisite outer shell unfilled, a measure of reactivity.

Trace Metals and Metalloenzymes: In Table XXVII is a partial list of some of the enzyme systems believed to contain a trace metal as a prosthetic group. The list is by no means complete and undoubtedly will be expanded in the future as enzymes are purified. According to Williams (235) and Najjar (236) there are two types. In one a specific element, and no other, is firmly combined or chelated with the protein apoenzyme for enzymatic activity; other metals may inhibit activity. The second is relatively less specific in that two or more metal ions, usually in the first transitional series, can be interchanged and the metal is more or less dissociable from the protein. Some of the peptidases were thought to have only partial specificity until the work of Emil Smith (140) strongly

suggested that metal ions considered interchangeable, such as magnesium, manganese and cobalt, are specific for enzyme activity and cannot be interchanged in the strict sense of the term.

Certain metalloenzyme systems need organic coenzymes (or vitamins) for activity. One possible example is pyridoxal phosphate which, according to Snell, requires a metal for the coenzyme to become activated (215). While the metal is not known, model systems constructed without the apoenzyme suggest that either copper, iron or aluminum could be the essential one (237). It is apparently so firmly bound that most metal-binding agents will not remove it Other well-known examples are riboflavin, where flavin-adenine-nucleotide is intimately bound with the oxidation and reduction of iron, and the copper flavinoid in acyl Coenzyme A-dehydrogenase. Other members of the vitamin B group in some cases may require metals for activity; magnesium with thiamine, and molybdenum with flavin-adenine-nucleotide, are examples.

In general, the active essential metals are divalent and in the first transitional group of the periodic table. Copper is essential for phenolic and catecholic oxidation and for fat metabolism. Manganese is required for peptide splitting and for carboxylation. In view of the high concentrations of zinc in tissues and the very few zinc enzymes found, carbonic anhydrase being the most prevalent, it is possible that others exist. The metallo-porphyrins are good examples of chelates· heme, the prosthetic group of hemoglobin, has iron chelated to four methyl pyrole rings; the iron porphyrins of the cytochromes and myoglobin; vitamin B^{12} has cobalt chelated in a porphyrin structure, and the porphyrin of chlorophyll chelates magnesium. There are several metalloproteins known; ceruloplasmin and hemocuprein contain copper, mercaptalbumins ap-

TABLE XXVII

EXAMPLES OF SOME METALLOENZYMES, MOSTLY MAMMALIAN*

	Essential Metal	*Other Activators*	*Organic Co-enzyme*	*Remarks*
Copper Enzymes				
Tyrosinase	Cu^{++}		?Pantothenic acid	0.1–0.3% Cu
Ceruloplasmin	Cu^{++}			0 32% Cu
Hematocuprein	Cu^{++}			Function undiscovered
Hemocuprein	Cu^{++}			
Hemocyanins	Cu^{++}			
Acyl Co A dehydrogenase	Cu^{++}		Flavin	
Proteolytic Enzymes				
Leucine aminopeptidase	Mn^{++}	Mg^{++}		
Glycylglycine dipeptidase	Co^{++}	Mn^{++}		
Glycylleucine dipeptidase	Mn^{++}	Zn^{++}		
Prolidase	Mn^{++}			
Carboxypeptidase	Mg^{++}			
Carnosinsase	Mn^{++}	Zn^{++}		
Dehydropeptidase	Zn^{++} (?)			
Arginase	Mn^{++}	Fe^{++}, Co^{++}, Ni^{++}		
Polypeptidases	Zn^{++} or Co^{++}			
Keto Acid Carboxylases				
α-ketoglutaric carboxylase	Mg^{++}	Mn^{++}	Diphosphothiamin	
Pyruvic acid oxidase	Mg^{++}	Mn^{++}	Diphosphothiamin	
Oxaloacetic carboxylase	Mn^{++}			
Oxalosuccinic carboxylase	Mn^{++}			
Carbonic anhydrase	Zn^{++}			0.31–0.34% Zn
Phosphatases (most)	Mg^{++}	Mn^{++} or K^{+}		
Acid	Mg^{++}			

* After Lehninger (267) and others (307, 245).

TABLE XXVII—(*continued*)

Alkaline	Mg^{++}	Zn^{++}, Co^{++}, Ni^{++}, Cd^{++}		
ATP-ase	Ca^{++}, Mg^{++}			
Hexosediphosphatase	Mg^{++}			
Transphorylase	Mg^{++} $(+K^{+})$			Phosphoenol-pyruvate to ADP
Flavokinase	Mg^{++}		Riboflavin	
Actomyosin	Ca^{++}			Inhibited by Mg^{++}
Arginine-ATP-transphorylase	Mg^{++}			
Phosphoglucomutase	Mg^{++}			
Hexokinase	Mg^{++}			
Enolase	Mg^{++} or Mn^{++}	Zn^{++}		
Dehydrogenases				
Phosphogluconic acid	Mg^{++}	Mn^{++}		
Isocitric	Mn^{++}			
Alcohol	Zn^{++}			
Oxidases				
Xanthine	Mo^{+VI}		FAD	0.03% Mo
Aldehyde	Mo^{+VI}		FAD	
Monamine	V^{+IV}			Only activator found†
Histaminase	?		Pyridoxal PO_4?	Metal not known
Decarboxylases				
5-hydroxytryptophan	Zn^{++}	Mn^{++}, Mg^{++}	Pyridoxal PO_4	
DOPA	Zn^{++}		Pyridoxal PO_4	Metal inferred†
Histidine	?		Pyridoxal PO_4	
Oxalacetate	Mn^{++}	Co^{++}		
Others				
Transaminase	?		Pyridoxal PO_4	Metal not known
Uricase	Zn^{++}			

† See Table XXIII, p. 126 and p. 154.

parently transport zinc and copper by imidazole binding, and gamma globulins contain various metals, some possibly bound to sulfhydryl groups. The discovery of hexavalent molybdenum as essential not only drew attention to heavier metals but was also the first example of a high valency metal in an enzyme. Therefore, higher valency metals in the first transitional group are not excluded from essential functions (Ti, V, Cr), nor are heavier ones.

The practice of suspecting the presence of a trace metal in an enzyme system by attempting to inactivate it with metal binding agents (cyanide, sulfide, azide, mercaptans, thiocyanate, ethylenediamine tetraacetate) may lead to false assumptions if the metal is more tightly bound to the enzyme than it can be to the binding agent. In the case of carbonic anhydrase, a known zinc metalloprotein, many strong chelating agents apparently fail to inhibit activity, although some binding agents do (238). Inhibition by sulfanilamide may be the result of zinc binding. Strange to say, zinc itself is a potent inhibitor, as are silver, gold, copper, mercury and vanadium. The kinetics of such reactions have not been described sufficiently to allow predictions as to different metals involved; purification of an enzyme now is the only real proof.

POSSIBLE COMPETITIONS BETWEEN ABNORMAL AND ESSENTIAL TRACE METALS

The validity of the Periodic Table appears established for physics, geology, chemistry and metallurgy, but until recently there has been little application of these disciplines to the biochemistry of disease. Substitution of one element of a periodic group for another, however, has been often demonstrated in specific mammalian tissues.

Substitution of One Element for Another: In group II B, radium, barium, strontium, calcium and beryllium all

have an affinity for bone; both strontium and beryllium can cause rickets, and beryllium displaces magnesium on phosphatases, inactivating them. Therefore all but magnesium are concentrated by one tissue. Similarly, two anionic and all cationic elements in group VII have been shown to be concentrated by the thyroid: iodine, astatine; manganese, technetium, and rhenium; those of the halide sub-group quite specifically (239-242). Likewise in group V A bismuth, antimony and arsenic are believed to displace phosphorus in phosphates Gold, silver and copper of group I B have strong affinities for each other, as does cadmium for zinc in group II B, complete separation of the two from ores is difficult and often too expensive for commercial purposes. Cadmium displaces zinc on human mercaptalbumin, while lead does not, presumably because the former two ions bind the same molecular group (the 16 imidazole groups), while the latter binds at a different site. Cadmium therefore has a higher affinity than zinc for this protein. Similarly, cupric ion is displaced from the sulfhydryl groups of bovine serum albumin by metals in the following order of affinity: $Hg^{++} > Pb^{++} > Cd^{++} > Zn^{++}$ (243). Among the anions, fluorine, chlorine, bromine and iodine are biologically interrelated, while selenium and tellurium of group VI A will displace sulfur in hair and nails, possibly in sulfhydryl groups. In group I A, radio-rubidium is used to measure potassium space (244)

Metalloenzyme Inhibitions: In spite of these obvious relationships in biological material, metalloenzyme competition by an extraneous metal has not been systematically studied. In Table XXVIII are shown examples of cases where an extraneous metal apparently displaces an active metallic prosthetic group. The list may be far from complete. At least two types of enzyme inhibition can occur.

TABLE XXVIII

SOME EXAMPLES OF INHIBITION OF METALLOENZYMES BY METALS

Enzyme	*Activator*	*Inhibitor*	*References*	*Remarks*
Alkaline phosphatase*	Mg^{++}	Be^{++}, Cu^{++}	298	Other inhibitors less effective
ATP-ase*	Ca^{++}, Mg^{++}	Be^{++}, Cu^{++}	298, 299	
Arginase*	Mn^{++}	Be^{++}	267	
Carbonic anhydrase	Zn^{++}	Cu^{++}, Ag^{++}, Au^{++} Zn^{++}, Hg^{++}, V^{+++}	238	Other metals (Cd^{++}) forming insoluble bicarbonates or phosphates may compete
Tyrosinase*	Cu^{++}	Au^{++}, Ag^{+}, Hg^{++}	216	
Leucine aminopeptidase	Mn^{++}	Cd^{++}, Cu^{+}, Hg^{++}, Pb^{++}	300	
Carnosinase*	Zn^{++} or Mn^{++}	Ca^{++}, Cd^{++}	301	
Xanthine oxidase	Mo^{+VI}	Cu^{++}, Hg^{++}, Ag^{+}, Pb, As	302	No other transition elements or Cd
Aldehyde oxidase	Mo^{+VI}	As	303	
Glutamic transferase	Mn^{++}	Cu^{++}	301	
Succinic dehydrogenase	Cu^{++} ?	Cd^{++}	238	
Choline oxidase	?	Cd^{++}	238	Metal not established
Prolidase	Mn^{++}	Co^{++}, Ca^{++}, Zn^{++}	305	
Glycylglycine peptidase	Co^{++}	Zn^{++}	306	
Phosphoglucomutase	Mg^{++}	Cu^{++}, Ag^{+}, Hg^{++}, Zn^{++}, Pb^{++}	238	

*Probably by specific displacement. For other examples, see Tables XXIII and XXVI.

One is when a heavy metal combines with sulfhydryl groups to inactivate the enzyme. Mercury, copper and silver will inactivate many enzymes which do not contain a metal (245). Presumably, the toxic effects of many heavy metals are due to this type of reaction. The second is when the essential metal is displaced by another, often of the same periodic group. Lerner has offered good examples of both types of reactions in respect to tyrosinase, essential for formation of melanin (246): "Metals which compete with copper: Increased melanin pigmentation is frequently observed when heavy metals such as arsenic, bismuth, iron, gold, silver, and mercury are deposited in the skin. Patients with hemochromatosis have relatively large amounts of iron and copper deposited in the skin. The most plausible explanation for these findings is that metals bind epidermal sulfhydryl groups and thereby release inhibition of tyrosinase. The increased tyrosinase activity results in increased melanin formation. However, if sufficient quantities of the metals mercury, silver, or gold are present they can replace the copper of tyrosinase to produce an inactive enzyme with resultant depigmentation. It is possible that the slight decrease in skin color produced by ammoniated mercury freckle creams is achieved *in* this manner." Six copper binding agents have caused depigmentation *in vivo* (247), most of them antithyroid drugs

Essential metals, such as copper, manganese, cobalt and zinc, can interact to inhibit the metalloenzymes of each. Excess enzymatic activity by a presumably abnormal metal can also occur. For example, chromium causes increased synthesis of cholesterol and fatty acids by rat liver (248); cadmium and cobalt enhance bacterial oxalacetic carboxylase, a manganous enzyme; vanadyl ion enhances monamine oxidase (Table XXIII). Thus, both stimulation and depression by abnormal metal are possible.

The effects of a series of metals on two enzymes possibly concerned in arterial hypertension are shown in Table XXIII. At the highest concentrations it is probable that inactivation of dihydroxyphenylalanine (DOPA) decarboxylase by metals was nonspecific or caused by sulfhydryl binding; at low concentrations the specific inhibition by cadmium and mercury may be the result of displacement of another essential metal. Since the coenzyme is pyridoxal probably with a metal, displacement of the chelated essential metal is the most plausible explanation of the mechanism of inhibition. If so, zinc may be the essential one. Obviously, high concentrations of cadmium in the kidney might cause serious metabolic alterations in the decarboxylation of several amino acids.

If interference of a single metalloenzyme system can be caused by another competing and inactivating metal, certain chronic diseases could ensue. As a theoretical example, if the molybdenum in xanthine oxidase were replaced by another in the same periodic group, for example, tungsten or chromium, and the enzyme so inhibited, gout might be produced. There is no evidence whatsoever that gout is due to tungsten or chromium but this is a theoretical possibility. Interference by an extraneous metal such as chromium, with manganous ion in the Krebs cycle would interfere with carbohydrate metabolism. Any one of these reactions could have profound and lasting results if a sizeable part of the total activity of the enzyme in the body were inhibited.

Simple Chelating Compounds: A great many organic compounds possess the ability to bind metals in more or less dissociable complexes. Many others form chelates in which two or more electron donors combine with the metal to produce one or more rings (*233*). The importance of chelation has long been appreciated in industry, but only

lately in biology, although the calcium citrate chelate is commonly used to prevent clotting of blood. All metalloenzyme reactions are believed to depend upon chelation.

Each chelating compound differs widely in its affinity for different metals. In Table XXIX are shown the stability constants of a number of common oxygen and nitrogen chelators with divalent metals of the first transitional group and with cadmium. Ten of these compounds are present in biological fluids. In general, an increase in tightness of structure is proportional to atomic number, reaching a peak at copper (or nickel) and decreasing thereafter. This fundamental property of most chelating agents must be in mind whenever they are used; in effect, this property means that a free ion having a higher stability constant with the chelator will displace a chelated metal with a lower constant. When the active groups are sulfur and other chelators, the pattern of metallic affinity is different (Table XXV).

Metal Binding: Simple metal binding is dependent either upon the tightness of the bond, the lack of dissociation of the dissolved salt, or upon the insolubility of the complex. Thus, complexes may be formed between metal and ammonia, metal and sulfhydryl, metal and cyanide or metal and hydroxide. The stability constants for transitional metal complexes in solution are usually lower than for chelates, although mercury has a fairly high affinity for CN, NH_3, OH and pyridine. The common law relating the stabilities of chelates of the first transitional group and atomic numbers appears to operate in the case of simple complexes of OH, CN, NH_3, and pyridine.

DRUGS AS CHELATING AGENTS

Most potent drugs may act through their abilities to chelate trace metals on metalloenzymes. Schubert states

(232): "The action of many drugs probably can be explained, partly or wholly, by their possession of groupings capable of binding metals. The drug, whether deleterious or helpful to the organism, inhibits or activates a physiological function in which a metal is required. Inhibition or activation may come about in several ways:

"1. The drug may chelate a metal ion needed for the activation or inhibition of an enzyme system and, hence, indirectly necessary for survival.

"2. The drug, by its chelating action, may facilitate the transport of a metal ion to its site of action, in some cases by the formation of a fat-soluble metal chelate.

"3. The chelating drugs may render available for metabolic purposes a metal ion which otherwise might remain in an inactive, insoluble form.

"4. The metal chelate may be readily excreted, thus providing a means of detoxification.

"Examples of drugs which may act through chelation by some of these actions are given below. Of further interest are the factors determining whether or not a metal-chelating drug will be effective, since these same factors are responsible for chemical specificity in biological systems. Knowledge that metal chelation is the basis of a drug's action facilitates considerably the development of new drugs, because it becomes possible to anticipate how the drug molecule can be modified to enhance its metal-binding properties. . . .

". . . In the case of salicylic acid, it is highly probable that metal chelation is important. This is shown by the fact that the m- and p-hydroxybenzoic acids which do not chelate are inactive as analgesic agents or against the fever and pain associated with rheumatic fever. It is not known which metal or metals are affected by salicylic acid, but it is known that the metals affected must belong to the

transition groups. Numerous derivatives of salicylic acid containing the o-carboxyl hydroxyl group are about as effective as salicylic acid, although they differ in dosage required and side effects. It might be anticipated that, physiologically, cortisone would have some resemblance to salicylates, as has been demonstrated experimentally. Terramycin and aureomycin reverse the Be inhibition of alkaline phosphatase through the formation of a complex ion with Be." He lists as examples: salicylic acid, adrenalin, terramycin, aureomycin, a thiosemicarbazone and cortisone. Penicillin forms insoluble salts with heavy metals.

Many chelating agents are fungicidal, antiseptic or bactericidal (233). Thirteen of nineteen common organic chelators of one or more transitional metals are listed by Martell and Calvin as effective against growth of B. subtilis with seven against growth of B. Coli. Likewise, 8-hydroxyquinoline of seven quinolines, and 26 substituted quinolines of 35, are effective against the growth of clostridium welchii, most of which inhibit streptococcus hemolyticus, staphylococcus aureus and B. Coli; less so proteus and pseudomonas pyocyaneus. Zinc and manganese appear to be bound, although the other essential metals, iron and cobalt may be involved. Apparently copper is *not*, for copper reagents in general are inert. Few are effective against pyocyaneus, an organism resistant to most antibiotics. The fungicidal properties of the oxines, so widely used in industry, is believed to be the result of their chelation with zinc, an essential metal for growth. Therefore bactericidal and fungicidal activity of many antiseptics and antibiotics may be functions of metal binding or chelation

The most popular and versatile of the recognized chelating drugs is ethylene-diamine tetraacetate (EDTA, Sequestrene, Versene), stability constants for which are shown in

TABLE XXIX

THE LOGARITHM OF THE STABILITY CONSTANTS OF SOME METAL COMPLEXES*

Ligand	log K_N									
	N	*Mg*	*Ca*	*Mn*	*Fe*	*Co*	*Ni*	*Cu*	*Zn*	*Cd*
$NH_2CH_2CH_2NH_2$ (En)	2	Small	Small	4 8	7 5	10.7	13.8	19 6	10.4	10.0
Histidine	2	—	—	7 7	—	13 8		18 6	12.8	—
$N(CH_2CH_2NH_2)_3$ (Tren)	1	—	—	5 8	8.8	12.8	14 8	18 8	14.6	12.3
$CH_2NH(CH_2CH_2NH_2)$										
$CH_2NH(CH_2CH_2NH_2)_2$ (Trien)	1	—	—	4 9	7 8	11 0	14.0	20.4	12.1	10.7
Glycine	2	6 5	1 4	6 6	8 0	8.9	11.1	15.4	9.7	8.6
Glycyl-glycine	1	1 1	1 2	—	—	3.5	4 5	6 0	3.8	—
$N(CH_2CO_2H)_3$ (Triac)	1	5 4	6.4	7 4	8 8	10.6	11.3	12 7	10.4	9.5
$CH_3N(CH_2CO_2H)_2$										
$CH_2N(CH_2CO_2H)_2$ (EDTA)	1	8 7	10 6	13 5	14 2	16 1	18 5	18 4	16.1	16.5
Oxalate	1	3 4	3 0	3 9	—	4 7	5.3	6.2	4.9	3 9
Tartrate	1	1 4	1 8	—	—	—	—	—	2.8	—
Salicylaldehyde 5-Sulphonic acid	2	—	—	—	—	5 6	6 6	9.3	5 4	—
Salicylaldehyde†	2	6 8	—	6 8	7 6	8 3	9 2	13.3	8 1	7.8
Acetyl acetone†	2	9 5	—	—	—	11 2	12.1	17.1	—	—
Polyphosphate (N = 2)	?	3 2	3 0	2 5	3.0	3 0	3 0	3.5	2.5	—
Hydroxyl ion	1	2 6	1 1	2 8	3 2	3 6	3.8	6.5	4.7	3.0
Dipyridyl	3	—	—	—	16 5	—	—	17.8	—	10 5
ortho-Phenanthroline	3	—	—	—	21 5	—	—	—	17 0	15.2
Riboflavin	?	—	—	3 4	7 1	3 9	4.1	6.6	3 6	4.7
Folic Acid	?	—	—	6 0?	7 9	8.1	9.0	7.8	7.5	6 7

* After Williams (235).

† The measurement of these stability constants was made in a mixed dioxan/water solvent, whereas the other measurements were all made in aqueous solution

Table XXIX. In addition to the transitional metals, many

not metabolized (249), and apparently enters cells (250), it provides a means for removing soluble ions from the body in the order of their stability constants. If an abnormal trace metal is to be removed, normal ones will accompany it according to the relative amounts and stability constants of each. Thus, EDTA is not specific for lead, for example, a current popular use, but will remove other ions with a higher constant such as copper and nickel and especially ferric iron EDTA will be inactive, however, if the metals in the body are more tightly bound or chelated to protein than to the drug. This relative chelating capacity of a sequestering agent and a metal in the body follows certain definite laws and explains the ineffectiveness of EDTA for removing most metals

An example of the effects of EDTA given intravenously to two patients is shown in Table XXX. Zinc was removed in sizeable quantities; other metals less so or not at all. The high excretion of zinc in the patient with the nephrotic syndrome found before the drug was given is probably explained by the excessive proteinuria, which carries combined zinc. There was no mobilization of lead, while

* EDTA makes a good chelating agent for clinical use, *for the following* reasons 1 The stability constants (Log K_s) for common but *important* loosely bound metals is low (Ba, Sr, Ca, Mg = 7 76-10 96). 2. The constants for more tightly bound metals is moderate (Mn, Fe^{++}, Co, Cu, Zn = 14.04-18.8) 3. The constants for several abnormal metals is high (*Hg* 21.8, V^{+++} 25 9, Fe^{+++} 25

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TABLE XXX

Renal Excretion of 13 Metals Before, During, and After Intravenous EDTA

Date	i.v. EDTA gm.	Urine Volume l	Urine Protein gm/l	Ti	V	Cr	Mn	Ni	Zn	Mo	Ag	Cd	Pb	Sn	Fe*	Cu*
				Parts (by weight) per billion parts of urine												
Normal Subjects		Mean		<3.8	<0.63	<0.64	<9.7	<2.8	<67	<14	0.80	<0.86	<5.7	<3.2		
Nephrosis																
11/3/54	0	1.55	—	2.0	3.1	0.17	13	3.2	360	5.0	0.74	2.9	0.80	13	570	330
2/25/55	0	2.66	2.6	0.37	<1.0	0.14	<5.0	0.75	360	3.6	0.59	1.3	3.4	22	560	—
2/26/55	0	2.15	2.4	0.16	<1.0	<0.05	<5.0	1.8	170	3.5	0.76	0.88	0.28	6.0	560	162
2/27/55	0	1.80	2.2	0.88	<1.0	<0.05	<5.0	2.2	370	3.2	0.54	2.5	0.60	14	660	230
2/28/55	0	2.36	1.6	0.95	<1.0	<0.05	<5.0	2.2	240	4.1	0.57	1.4	0.22	6.4	460	265
Mean	0	2.24	2.2	0.59	<1.0	<0.07	<5.0	1.7	285	3.6	0.62	1.5	1.1	12	560	219
3/1/55	3	1.81	2.4	1.1	<1.0	0.11	21	2.4	1900	3.0	0.36	<0.5	0.27	2.5	1050	180
3/2/55	3	2.01	2.8	2.0	<1.0	0.35	12	4.0	1400	2.2	0.32	<0.5	0.07	2.2	1070	162
3/3/55	4	1.46	3.2	0.50	<1.0	7.3	15	16	2200	2.4	0.38	2.8	0.70	4.8	1930	187
3/4/55	0	1.97	2.4	0.73	<1.0	0.12	8.5	2.4	1200	1.2	0.37	4.0	0.04	3.4	1450	385
Mean	2.5	1.81	2.7	1.1	<1.0	2.0	14	6.2	1675	2.2	0.36	1.9	0.27	3.2	1375	229
3/5/55	0	1.73	3.2	1.3	<1.0	<0.05	<5.0	3.0	640	<0.5	0.43	3.6	0.13	3.9	—	385
Normal Female	39															
10/6/55	0			2.7	7.9	6.75	<6.0	1.15	17	7.0	0.4	<1.02	70.1	10.25		
10/8/55	0			—	1.1	1.8	<5.0	2.9	25	16	0.51	<0.5	2.0	14.25		
10/11/55	0			1.8	7.4	4.0	Tc	1.75	50	13.25	0.34	0.85	215	85		
Mean				1.5	5.5	4.2	±4	1.9	31	12.08	0.42	±0.79	95.7	36.5		
10/16/55	3			0.65	<0.5	0.78	Tc	3.1	46	12	0.33	0.68	7.0	13		
10/17/55	3			16	2.35	1.45	16	2.0	490	9.25	0.43	0.9	26.5	3.0		
10/18/55	3			8.25	1.8	1.75	17.5	1.75	650	9.25	0.43	0.58	55	5.5		
10/20/55	3			5.0	1.55	1.5	27	1.6	800	13.5	0.43	14	87.5	5.25		
Mean				7.46	±1.55	1.37	±15.1	2.11	496.5	11.0	0.41	4.04	44.0	6.69		

From data of Perry and Schroeder (181). The normal subjects were 15 laboratory workers. Note the increases in chromium, manganese, nickel and iron in the nephrotic patient, in titanium, manganese and cadmium in the normal woman, and the enormous increases in zinc in both subjects. The limiting factor of this drug is obviously zinc deficiency. Note also the failure of lead to move. The high initial excretions of zinc and copper in the nephrotic patient represented protein bound metal in urine.

* The iron determinations were done by Dr. Reubenia S. Dubach, and the copper by Dr. Clark J. Gubler.

eight metals, almost certainly present in a strongly bound form in their tissues, did not change.

BAL (2,3-dimercaptopropanol), a straight chain dithiol, binds the following heavy metals in a chelate: zinc, chromium, cadmium, nickel, lead, antimony, arsenic, bismuth, copper, mercury, gold (251). Substitution complexes on the sulfhydryls are formed. In the case of cadmium, at least, these are dissociated in the kidney and may result in cadmium nephritis, a reflection of the greater binding capacity of renal tissue for cadmium than BAL. Citrate, a chelating agent used for lead poisoning, is metabolized by the body and is therefore relatively ineffective. A list of some representative binding and chelating agents is shown in Table XXXI. Their use in medicine is only beginning. For example, all antithyroid drugs have this common property, suggesting their probable action.

These considerations open up a wide field of thought on the mechanisms of disease and of drug actions. Similar conclusions can be drawn when late toxic reactions of drugs are compared with structure. The common denominator of the offending drugs appeared to be in chelation.

Drug Reactions: Late systemic reactions to drugs affect several organs and systems, of which blood dyscrasias, hepatitis and polyarteritis are the most serious (252). Most of the drugs causing fatal agranulocytosis, as listed by [illegible]

[illegible], procaine amide and Tapazole, containing pyridines, amines, amides, nitroso, or sulfhydryl groups (253). Their solubilities and specificities for heavy metals, however, are not known to our knowledge. Nonfatal leucopenia has occurred with arsenical compounds, gold salts, thiouracils, hydantoins, salicylates, sulfonamides, streptomycin and thiosemicarbazone, which can displace or bind

TABLE XXXI

SOME EXAMPLES OF CHELATING AND METAL-BINDING DRUGS (232, 233, 253)
(OTHER THAN ANTIHYPERTENSIVE AGENTS)

Drugs Used To Remove Metals	Reference
EDTA	233
BAL	251
Citric Acid	235
Antithyroid Agents†	294
Thiourea	247
Thiouracil	247
2-Mercaptoimidazole* (Tapazole)	253
2-Aminothiazole*	253
P-Aminobenzoic acid*	253
Sulfonamides	233
L-5-vinyl-2-thio-oxazolidone	294
Antibiotics†	
Sulfonamides	233
Penicillin (and penicillamine)	253
Chloramphenicol*	253
Streptomycin*	253
Isoniazid	296
Thiosemicarbazone*	253
P-Aminosalicylic acid	233
Analgesics and Antipyretics†	
Aminopyrene	233
Antipyrine	253
Phenylbutazone*	253
Phenacetylurea*	253
Salicylic acid	233
Miscellaneous†	
Bis(diethylthiocarbamyl) disulfide (antabuse)	297
2-Acetylamino-1,3,4,thiadiazole-5-sulfonamide (Diamox)	233
Drugs Containing Specific Groups†	232, 233, 234
Pyridine	
Thiol or Mercaptan	
Carbazide	
Diazine	
Thiazol	

* Contains metal binding groups, affinities not known

† Drugs causing late toxic reactions.

TABLE XXXI—(*continued*)

Nitrite	
Thiocyanate	
Pyrocatechol	
Quinaldine	
Hydantoin	
Hydrazine	
*Chelating Chemicals***	
Phytic Acid	
2-ketogluconic acid	
Glycerophosphates	
Potassium gluconate	
Gallates	
Rubeanic acid and derivatives	
Guanidine carbonate	
Potassium ethyl xanthate	
Dimethyl glyoxime	
Uracils	
Oximes	
Diphenyl carbazide	
Diphenyl thiocarbazone	
Potassium thiocarbonate	
Cupferron	
Adipoin	
Some Reagents for Analysis of Metals	256
Zn Ferric cyanide	
8-hydroxyquinoline	
Quinaldinate	
Sn Dinitro-diphenylamine sulfoxide	
Toluene dithiol	
Ag P-dimethylamino-benzalrhodamine	
Ni γ-benzil-dioxime	
Dithiooxalate	
Dithiol	
Mo Thiocyanate	
Cu Quinosol	
Pyridine thiocyanate	
Cd β-napthoquinoline	
Thiourea	
Benzoin-oxime	

** From chemical catalogues

trace metals. The properties of the few other drugs causing this disorder are not known. Even the more unusual cases of leucopenia are due to such metal-binding agents as barbiturates, chloramphenicol, isoniazid, demerol, phenothiazines, novalgin, pamaquine, penicillin and phenurone, which appear to possess the requisite metal-binding groups or to form insoluble metallic salts.

Alexander's list of drugs reported to cause aplastic anemia contains eight of the above agents, with the addition of such possible metal-binding agents as quinacrine, hydralazine, mercurial diuretics (both mercury and amide are present in mercuhydrin), novurone and para-aminosalicylic acid. The drugs causing thrombocytopenic purpura include eleven of the above, with the addition of sedormid, procaine, quinine and quinidine containing either similar groups or quinoline. In the case of quinine and quinidine, the quinoline structure is not such as to have chelating properties, the requisite group being on the 4 position, while 8-hydroxyquinoline is a strong chelating agent. Unless the ring structure is broken in the body to form quinolinic acid, the mechanism of action is probably not dependent upon chelation. Hepatitis has been caused by 17 of the above drugs and by acriflavine, cortisone and carbazone, all of which contain metal complexing or sequestering groups.

Aside from proteins and undefined extracts of plant and animal tissues, many of the same drugs appear in the list of causes of what Alexander calls the "serum sickness pattern" (252). Twenty-one of the above drugs are listed, with the addition of thiocyanate, ACTH (which may mobilize zinc and contain sulfhydryl), bismuth, two new antibiotics structurally unidentified, and chlorpromazine, which obviously has metal binding properties when hydrolyzed. When a comparison is made with the substances

causing shock, 13 new ones appear which do not have this property and 13 of the above are represented. Bronchial asthma, caused by 36 agents, of which 19 are of plant or animal origin and unidentified structurally, is caused by 14 containing possible metal complexing groups or metals. A similar situation appears among the agents causing severe late toxic skin reactions such as eczema, urticaria, exanthemata, exfoliative dermatitis, bullous eruptions and the like. Metals and binding agents appear frequently when the chemical structure is known.

Curiously enough, serious local and systemic reactions are rare or absent among the drugs not containing metal-reactive groups or producing them only on extensive hydrolysis. Sulfobromphthalein, decholin, paredrine, ether, boric acid, Banthine, menthol, quotane, diocaine, chloral hydrate, morphine, opium, codeine, digitalis are examples. On the other hand, barbituric acid, the basic constituent of many sedatives, and a pyridine compound, forms salts with metals. Metal binding by sulfanilic acid is well known (233). The instability of hydantoin, hydrolyzing to metal-binding hydantoic acid, the metal binding properties of pyridines, nitroso groups (dinitrophenol is a good example), cyanides, amine and sulfhydryl groups, semicarbazides, dicarboxylic acids, thiols and sulfur-containing structures appear to be related to many forms of "drug sensitivity." Therefore, it is possible that trace metals may be involved in many reactions of sensitization and perhaps even in some forms of allergy. BAL (2,3-dimercaptopropanol) for example, is a potent contactant. Although drug reactions vary widely in frequency, such agents as dinitrophenol being very active and amines relatively inactive, metalloenzyme disturbances cannot be excluded as causes. It will be noted that the more metal binding groups on the soluble sulfonamides (pyridine, thiazole, succinate, etc.) the more likely

the agent is to produce late generalized reactions. The interested reader can find many examples of this apparently general phenomenon by comparing structure (253), metal binding power (233) and ability to produce late reactions (252).

The author by no means wishes to imply that the phenomena of hypersensitivity, allergic and immune reactions, and anaphylactic shock are the result of trace metal chelation. The mechanisms of these reactions, involving altered proteins, have been studied extensively enough to exclude trace metals as being primarily responsible. Late toxic reactions to drugs, however, may well be caused either by metal imbalances or sensitivity. Thrombocytopenia induced by quinine is an example of the latter. Obviously, the problem should be studied further from this viewpoint.

ESSENTIAL TRACE METALS IN MAN

To be essential for mammalian metabolism, the trace metals under consideration should be able to form chelates and to be reactive. They should be demonstrable in human tissues, both of infants and of adults. They should be found in sea-water, for life began in the sea, and in plants. They should demonstrate activity on enzyme mechanisms, especially to accelerate reactions. We can apply these criteria to the metals actually found, examining the most logical ones (Table XXXII).

In Table XXXIII are shown the metals of interest found in sea-water. In general those of highest concentration are more prevalent in plants and animal tissues. The relative composition of sea-water, however, has probably changed since life began in the primitive ocean; only those elements present when amphibians left the ocean

TABLE XXXII

TRACE METALS FOUND IN MAN AND THEIR PROBABLE ROLES

Essential	*Possibly Essential*	*No Known Metabolic Function*	*Metabolic or Antimetabolic*	*Not Found But Antimetabolic*
Cobalt	Aluminum	Barium	Bismuth	Antimony
Copper	Strontium	Boron	*Cadmium*	Arsenic
Iron	Vanadium	Cesium	*Chromium*	Beryllium
Manganese		Gallium	Gold	Thallium
Molybdenum		Lanthanum	*Lead*	
			Nickel	
Zinc			Silver	
		Tin	*Titanium*	

Those in italics may be implicated in chronic diseases, especially cardiovascular, because of their prevalence, concentrations, or known functions on enzyme systems.

and satisfying certain criteria for reactivity in enzyme mechanisms can be expected to have become essential for metabolism. We cannot say that living cells have learned to use new and less reactive elements in enzyme systems by a process of adaptation; the basic structures of atoms have not changed and life began by using the most suitable ones.

Because all food comes eventually from plants, an examination of the metallic content of plants is necessary; local pastural variations can be neglected. No metal can be expected to be "essential" for animals which does not occur in plants or in water. In Table XXXIII are the metals of interest in plants Little aluminum, nickel, and no cadmium, tin, silver, gold, titanium, lead or mercury is to be expected in animal tissues, while vanadium and the five known essential metals will be found. Obviously, if domestic animals or man show appreciable quantities of those which do not appear in plants, they must have come from unnatural sources.

To be classed as "abnormal" for our thesis, a metal:

TABLE XXXIII

TRACE METALS IN SEA WATER, %*

(Also found in plants, animals and man (256, 257, 231, 254).)

	Seawater		Essential for Plants	Found in American Tissues			Essential for Mammals	Possible Contaminant	
	Factor	×10⁻		Infants	Adults	Adult Urine		from Soil	from Civilization
Mg	1.3	1	+	+	+	+	+		
Sr	1.3	3	?	+	+		+?		
B	4.5	4	+	+	±		?		
Rb	2 0	5	?	?	+				
Zn	5 0	6	+	+	+	+	+		
Fe	5 0	6	+	+	+	+	+		
Cu	2 0	6	+	+	+	+	+		
Al	5	5	0	+	+	?	?	+	+
Pb	5.0	7	0	+	+	+	0		+
Mn	4.0	7	+	+	+	+	+		
Ni	3.0	7	0	±	±	+	0	+	+
Sn	3.0	7	0	+	+	+	0	+	+
Co	1 0	7	+?	+	+		+		
Mo	1 0	7	+	+	+	+	+		
Ti	<1.0	7	0	0	+	+	0?	+	
V	5 0	8	+?		+	+	+?		
Hg	3.0	9	0		+		0		+
Ag	n	8	0	+	+	+	0		+
Au	4.0	10	0	0	±		0		+
Cd	Trace		0	0	+	+	0		+
Cr	Trace		0	+	+	+	0	+	+

0 = Strong evidence against element being essential. ? = Cannot be excluded at present

* After Vinogradov (255).

a) should be found in human tissues from some areas of the world and not from others; b) should not be found in plants or wild animals; c) should affect some metalloenzymes; d) preferably should not be in the tissues of young infants; e) should be introduced by the habits of Western Civilization into foods or beverages as a result of processing, transportation or manufacture, and f) should be poorly excreted, cumulative and preferably showing organ specificity.

Concentrations of the Essential Trace Metals in Man: Although many analyses have been done by various methods for single or several elements in blood, tissues and urine (254-257), the first extensive systematic investigation on the content of both essential and "abnormal" trace metals in human tissues was made by Tipton and her co-workers. Using spark spectrographic methods with indium as an internal standard and densitometric photoelectric recording of plates, Tipton analyzed 258 tissues from 24 persons dying suddenly in various areas of the United States for 18 metals (almost 4500 analyses) (231). A preliminary analysis of 42 autopsies from various places in this country showed similar but less quantitative results (258), while in a later series the findings were essentially the same (259).

In Table XXXIV are the mean concentrations in various tissues of the essential elements, manganese, cobalt, copper, zinc and molybdenum, calculated roughly for total bodily amounts. Zinc is the most prevalent of the normal group, in several times the concentration of any of the others. Essential cobalt was found in only five bodies sparsely scattered in small concentrations, probably because of methodological limits and its presence in very minute quantities. These *results* appear comparable to those of Griffith *et al.* for copper, zinc, and manganese on

TABLE XXXIV

Concentrations and Contents of "Essential" Trace Metals in Human Tissues (Wet Weight) (211)

Organ	Weight* Kg	Mo mg/Kg	Mo Total	Cu mg/Kg	Cu Total	Zn mg/Kg	Zn Total	Mn mg/Kg	Mn Total	Co† mg/Kg	Co† Total	No.
Adrenal	0.02	0.34	0.007	1.7	0.03	18.1	0.4	0.18	0.004			17
Aorta		0.17		1.96		20.1		0.33				9
Bladder	0.03	0.35	0.01	1.40	0.04	16.6	[illegible]	0.12	0.02			4
Brain & Cord	2.1	0.40	0.8	10.6	11.0	16.8	31.4	(0.21)	0.44			7
Heart	0.3	0.1	0.03	4.00	1.2	49.1	15.0	0.21	0.06			21
Stomach & Intestine	2.0	0.32	0.64	3.0	6.0	26.2	46.4	0.15	0.3			11
Kidney	0.3	0.4	0.1	2.76	0.82	67.2	20.1	0.61	0.2	0.20	0.06	32
Liver	1.5	1.13	1.6	10.6	15.9	68.4	102.6	1.62	2.4	0.8	1.2	34
Lung	0.7	0.6	0.42	4.5	3.2	18.1	12.6	(0.18)	0.12			26
Muscle	28.0	0.14	3.92	1.53	42.9	70.0	196.0	(0.41)	11.5	0.24	6.72	33
Pancreas	0.1	0.74	0.07	3.0	0.3	41.0	4.1	(0.21)	0.02	0.22	0.02	22
Prostate	0.05	0.24	0.01	4.72	0.02	155.0	7.8	(0.30)	0.01			22
Spleen	0.2	0.52	0.1	8.7	1.76	21.3	4.6	(0.13)	0.03			8
Testis	0.02	0.19	0.005	2.1	0.04	13.8	0.27	(0.12)	0.01			24
Thyroid	0.03	0.48	0.013	3.5	0.1	36.6	1.1	—	—			13
Skin	4.4											9
Skeleton	19.0											
Adipose Tissue	7.8	0.41	4.92	4.6	55.2	43.8	515.6	0.27	3.24	0.3	3.6	
Other Tissue	7.8											
Sub. Total, known (mg.)			5.762		93.93		435.37		13.134		8.03	
Total with estimated skin and other soft tissue at mean value × 12 Kg. (mg.)			10.682		149.13		960.97		18.374		11.6	
Specimens lacking metal		0		0		0		56		234		

Figures in parentheses indicate element missing in two or more samples. Mn, Cu, Zn were present in every sample. Mo was absent in one aorta and bladder, 3 stomachs.

* For 70 Kg. man according to Forbes et al. (203)

† In only 5 of 26 bodies

the basis of dry tissue in a much larger series (260).

Some organs concentrate certain metals, others do not. Zinc was found in every organ in concentrations of 4.4 to 300 mg./Kg., being far highest in prostate, then muscle, liver, kidney and heart, and lowest in adrenal, bladder, brain, testis, lung, and intestine. Copper was concentrated in brain, liver and spleen, being lowest in muscle, adrenal, aorta, intestine and testis. Manganese, in much smaller amounts, was concentrated especially in liver, with pancreas, lung, spleen and thyroid following quite far behind; lowest organs were heart, muscle, testis and aorta. Three of these four metals were found in all 258 specimens examined. Molybdenum was absent in only half of the samples of muscle and testis, a third of those of pancreas, thyroid and lung, most prostates and all but one brain, but was found in concentrations of more than 0.13 mg./Kg. in all heart, kidney and liver samples, being by far the highest in liver. In the concentrations detectable, molybdenum apparently is not essential for metabolism in all organs, but three of the others may be.

Sources and Turnover of Essential Metals: All of the essential trace metals are found to a greater or less extent in plant and animal tissues (Table XXXIV), derived from the soil. Cobalt is probably the least concentrated. Soils vary widely in their contents of trace elements and disorders due to deficiencies or excesses have been recognized in both plants and animals. Semi-quantitative trace mineral analysis is a recognized practice in the evaluation of soils for farming. The following was summarized from Monier-Williams (256) and Marston (261).

Manganese: The largest sources are in the following foods with above 30 mg./Kg.: oatmeal, whole meal flour, bran, soy bean meal, cocoa, cloves, chestnuts, pepper, maple sugar; tea contains 150 to 900 mg./Kg. With lesser con-

TABLE XXXIV

CONCENTRATIONS AND CONTENTS OF "ESSENTIAL" TRACE METALS IN HUMAN TISSUES (WET WEIGHT) (231)

Organ	Weight* Kg	Mn mg/Kg	Mn Total	Cu mg/Kg	Cu Total	Zn mg/Kg	Zn Total	Mo mg/Kg	Mo Total	Co† mg/Kg.	Co† Total	No.
Adrenal	0.02	0.24	0.005	1.7	0.03	15.3	0.3	0.18	0.004			17
Aorta		0.19		1.96		20.2		0.53				5
Bladder	0.02	0.25	0.05	3.40	0.68	16.6	3.3	0.12	0.02			4
Brain & Cord	2.1	0.40	0.8	10.6	21.0	16.8	21.4	(0.21)	0.44			7
Heart	0.3	0.1	0.03	4.09	1.2	49.2	15.0	0.23	0.06			23
Stomach & Intestine	2.0	0.32	0.64	3.0	6.0	23.2	46.4	0.15	0.3			11
Kidney	0.3	0.4	0.1	2.76	0.82	67.2	20.1	0.63	0.2	0.20	0.06	22
Liver	1.5	1.13	1.6	10.6	15.9	68.4	102.6	1.62	2.4	0.8	1.2	24
Lung	0.7	0.6	0.42	4.5	3.2	18.3	12.6	(0.18)	0.12			24
Muscle	28.0	0.14	3.92	1.53	42.9	70.0	196.0	(0.41)	11.5	0.24	6.75	23
Pancreas	0.1	0.74	0.07	3.0	0.3	41.0	4.1	(0.21)	0.02	0.22	0.02	22
Prostate	0.05	0.24	0.01	4.79	0.02	155.0	7.8	(0.36)	0.02			22
Spleen	0.2	0.52	0.1	8.7	1.74	22.3	4.4	(0.17)	0.03			8
Testis	0.02	0.19	0.004	2.1	0.04	13.8	0.27	(0.12)	0.02			24
Thyroid	0.03	0.48	0.013	3.5	0.1	36.6	1.1	—	—			13
Skin	4.4											9
Skeleton	19.0											
Adipose Tissue	7.8	0.41	4.92	4.6	55.2	43.8	525.6	0.27	3.24	0.3	3.6	
Other Tissue	7.8											
Sub Total, known (mg.)			5.762		93.93		435.37		15.134		8.03	
Total with estimated skin and other soft tissue at mean value ×12 Kg (mg.)			10.682		149.13		960.97		18.374		11.6	
Specimens lacking metal		0		0		0		56		234		

Figures in parentheses indicate element missing in two or more samples. Mn, Cu, Zn were present in every sample. Mo was absent in one aorta and bladder, 3 stomachs.

* For 70 Kg. man according to Forbes et al. (293).

† In only 5 of 24 bodies.

may also be important in hemoglobin formation. A copper enzyme, ceruloplasmin, is found in concentrations of about 34 mg. per 100 ml. of serum. Several phenolic oxidases depend upon copper; pigmentation may be related to the content in skin and hair follicles. Copper is quite well retained by the body with some dependency upon intake, being slowly eliminated by way of the feces. Gallstones contain large amounts. No chronic copper poisoning has been described in human beings Human milk is extremely low in content, 0 04 mg./Kg. As a rule, American foods contain adequate amounts, sometimes an excess, since many insecticides and fungicides contain copper. The largest amounts, 10 mg /Kg. or more, are found in tea, coffee, cocoa, chocolates, nuts, liver, shell fish, especially oysters, tomatoes and yeast. The least is found in milk, butter, cheese, refined sugar, honey, margarine, lard and suet.

Zinc. This most prevalent of the trace metals in the human body is present in large quantities in most organs, as seen in Table XXXIV. It is found in foods and is a requirement of plants, bacteria and fungi. Most modern fungicides are zinc chelating agents. Deficiency in soils causes diseases of both plants and animals, although its prevalence makes animal diseases more uncommon. Foods with over 50 mg /Kg. are wheat germ, bran, oysters, beef livers, gelatin and dried eggs; those which contain the least amount are fruits, chestnuts, green vegetables and fish Chronic poisoning in man is not known. There have been several outbreaks of supposedly acute poisoning from foods stored in zinc-lined receptacles, but the contamination of zinc by cadmium makes it questionable that zinc itself was the cause, symptoms of zinc and cadmium poisoning are identical, i.e., violent gastroenteritis, and zinc poisoning is most difficult to produce in animals.

centrations are green vegetables, nuts, rice and barley; of considerably less content are meats, legumes, and many organ tissues. Dairy products and fish are low in manganese and coffee contains extremely little. It has been estimated that about half the intake of adults in Britain during the winter came from tea. The minimum daily requirement for man has been variously set at 4.6 to 10 mg., about 0.01 mg. per day being excreted in the urine. In view of the small body pool, approximately 11 mg. according to the method of analysis (Table XXXIV), this high requirement may reflect the poor absorption of manganese from the gastrointestinal tract. Large amounts may be given daily, up to 1.0 Gm. per day of the citrate or glycerophosphate, without signs of toxicity and apparently without excessive absorption. While deficiency in man has not been described, a reasonable assumption that it might occur can be postulated, especially if conditioned by competing metals or affected by drugs. Toxicity from ingested manganese has not been described, although inhaled dust can cause Parkinsonian symptoms and occasionally cirrhosis of the liver.

Cobalt: Present in vitamin B_{12} as a porphyrin chelate, this element is essential for maturation of red blood cells, but has no other known function in man. It is rapidly excreted both in urine and feces and apparently does not accumulate. It may not be readily absorbed in man. An excessive amount produces polycythemia in the rat, dog, frog, mouse, guinea pig and sheep. While the amounts in food are not well known, traces occur in vegetables, fruits and cereals; 0.5 mg./Kg. in legumes and as little as 0.003 mg./Kg. in white flour. In view of the small body pool, deficiency in man is possible, but unproven. Cobalt is a vasodilator in man (262) and in the rat (183).

Copper: An essential element in cell respiration, copper

high content of iron in their livers. Apparently the bacteria in the rumen synthesize vitamin B_{12} when cobalt is present; high requirements are indicated by the large doses of the vitamin necessary to cure this disease. Horses and pigs raised in the same deficient areas are not affected, as their requirements are lower. Bacterial synthesis in the colon, as occurs in man, apparently does not lead to absorption of this vitamin; therefore it must be ingested as such. *Copper* deficiency has been implicated in certain anemias in infancy but no known diseases in adults have been described. Anemia has been produced in laboratory animals along with a slow rate of growth; impaired absorption of ingested iron, impaired mobilization of iron from tissues, and impaired utilization of iron for hemoglobin synthesis have been found, as well as low *cytochrome* oxidase activity of the bone marrow. Cattle grazing on copper-deficient pastures show depigmented, abnormal hair, develop cachexia, anorexia and anemia, their bones become fragile, reproduction and milk production is decreased and they frequently die of cardiac failure; young animals may become ataxic. Sheep show defective keratinization and hypochromic anemia; lambs born of copper deficient ewes develop "swayback," and ataxic and paralytic diseases characterized by diffuse demyelinization of the central nervous system. Depigmentation has been produced in many species Excesses or deficiencies of other trace elements may influence the disorders in cattle and sheep, especially of cobalt and molybdenum. *Molybdenum* deficiency prevents fixation of nitrogen by soil bacteria, [illegible]

[illegible] of the esophagus *in rats* (265)

Molybdenum: The newest of the essential elements to be found necessary in human and animal metabolism, molybdenum plus a flavin are necessary for the metabolism of xanthine to uric acid by xanthine oxidase and the oxidation of aldehydes by liver. It is essential for the fixation of nitrogen in the soil by nitrogen fixing bacteria. Molybdenum is present almost universally in fertile soils and in plant and animal tissues. Its toxicity resembles that of selenium poisoning; excesses in soils affect ruminants rather than horses and pigs, producing a disease characterized by chronic diarrhea called "teart." Copper fed to animals prevents molybdenum poisoning. An examination of the periodic table indicates that molybdenum is unique in that it is next to the heaviest element essential for mammalian metabolism and occurs in the hexavalent form. Whether or not deficiencies occur in man is not known; the body pool is small.

Specific Metal Deficiences (256, 261):* Actual deficiences of some metals in man are not inconceivable, although no true deficiency (other than iron) has been described. Lack of manganese kills rabbits; deficiency in rats causes failure of male reproduction and a high mortality rate in the young. Hen's eggs do not hatch well; perosis or "slipped tendon" with enlargement and malformation of the tibio-metatarsal joint and arrested growth of long bones, possibly due to low bone phosphatase, is caused by deficiency of this element in growing chicks. Pigs and rabbits also show bone affections, suggesting that it may be related to the growth or health of bone and joints.

Cobalt deficiency in soils causes enzootic marasmus, or Bush Sickness, in ruminants, characterized by impaired growth, anorexia, weakness, emaciation and anemia, with

* The reader is referred to Moore's recent critical and inclusive discussion of this subject (263).

TABLE XXXV

CONCENTRATIONS AND CONTENTS OF "ABNORMAL" TRACE METALS WITH ORGAN SPECIFICITIES (WET WEIGHT) (231)

Organ	Cd mg/Kg	Cd Total mg	Al mg/Kg	Al Total mg	Ti mg/Kg	Ti Total mg	Pb mg/Kg	Pb Total mg	B* mg/Kg	B* Total mg.
Adrenal	1 24	0 02	4 41	0 09	0 52	0 01	1 04	0 02	(0 39)	0.008
Aorta	1 09		9 09		0 75		1 05		(0 19)	
Bladder	(0 93)	0 19	2 53	0 5	0 21	0.04	0 39	0 08	(0 26)	0.05
Brain	0		3 55	1 1	(0 07)	0 14	0 31	0 62	0	
Heart	(1 74)	0 52	2 51	0 75	0 13	0 03	0 98	0 29	—	
Stomach & Intestine	1 20	2 40	3 25	6 50	0 44	0 88	0 58	1.16	(0.26)	
Kidney	33 1	9 93	1 80	0 54	0 14	0 04	1 27	0 38	—	
Liver	3 60	5 40	2 55	3 83	0 26	0 39	2 04	3 06	—	
Lung	(1 73)	1 21	30 8	21 6	7 65	5 36	1 21	0.85	—	
Muscle	(1 78)	49 8	3 01	54 2	0.48	13 4	0 71	19 9	—	
Pancreas	2 10	0 21	2 67	0 27	0 18	0 02	1 32	0 13	(0 41)	0 04
Prostate	(1 55)	0 03	5 53	0 28	1 51	0 03	0 29	0 01	—	
Spleen	(1 96)	0 39	3 34	0 67	0 31	0 06	1 33	0 27	(1.20)	0 24
Testis	(1.31)	0 03	3 87	0 08	0 21	0 004	0 67	0 01	—	
Thyroid	2 08	0.06	5 12	0 15	0 37	0 01	0 50	0 02	0	
Skin, Skeleton, Adipose Tissue, Other Tissue	3.88	46.6	5.35	64 2	0 89	10.68	0 90	10 8	(0.18)	2.16
Sub Total, known (mg)		70 24		96 56		20 46		26 80		0 338
Total with estimated skin and other soft tissue at mean value ×12 Kg. (mg)		116 84		160.76		31.14		37 60		2 498
Specimens lacking metal	76		3		11		0		159	

Figures in parentheses indicate element missing in two or more samples.
* Half or more of specimens only.

ous junctions. These signs are more like those of pyridoxine deficiency. It is doubtful that zinc deficiency ordinarily can be produced in man, except on very low intakes or during excessive proteinuria, during which loss of protein-bound zinc can occur. Some of the symptoms of beri-beri have been thought to be manifestations of zinc deficiency caused by low intakes. The patient shown in Table XXX exhibited acute pyridoxine deficiency twice when EDTA was given intravenously (181); probably his excessive urinary loss of protein-bound zinc added to the zincuretic effect of EDTA resulted in deficiency of the zinc chelated to some pyridoxal enzymes (Fig. 20, p. 231).

"ABNORMAL" TRACE METALS IN MAN

In Table XXXV are the concentrations and contents of the five presumably "abnormal" trace metals showing some organ specificity. We observe the following: Aluminum was not found in three hearts but was in every other organ examined, almost always in concentrations of over 1 mg./Kg., and in all but six, in over 3 mg./Kg. It was selectively concentrated in lung (perhaps by inhalation), with a third as much in aorta and a sixth or less in prostate, stomach, thyroid and adrenal; lowest values were in kidney. Amounts were higher than those of any essential metal save zinc. Cadmium appeared in kidneys in very high concentrations, with liver, pancreas, thyroid containing a tenth as much. Titanium appeared in lung (perhaps by inhalation), with prostate a poor second and a relatively even distribution in the other organs. Lead appeared highest in liver, pancreas, spleen, kidney, adrenal and aorta; lowest in stomach, brain and bladder. The less frequently found boron appeared to be concentrated in some spleens. On the other hand, little evidence of concentration in any one organ was found in the cases of the

ubiquitous elements tin, nickel, chromium, and silver (Table XXXVI).

The obvious conclusions are that relatively large amounts of cadmium are in American kidneys, and aluminum and titanium in lungs, while other metals are more or less evenly distributed. Furthermore, there is, weight for weight, more of several abnormal metals in most organs than normal ones of high biological activity, such as manganese, copper, and molybdenum. On the basis of mass alone, these three tables show the following, when the metals are arranged according to the periodic table. Silver is present in amounts equal to 2.2 per cent of copper, cadmium equal to 12 per cent of zinc (50 per cent in the kidney), chromium equal to 61 per cent of molybdenum (and is more prevalent), nickel equal to 140 per cent of cobalt, while there is more titanium, tin and lead than manganese, molybdenum and cobalt, and there is more aluminum than copper. Thus the order in decreasing amounts is *Zn*, Al, *Cu*, Cd, Pb, Ti, Sn, *Mo*, Ni, *Co*, Cr, *Mn*, Ag, B, according to the present estimate (essential ones in italics). Traces of gallium were found in most lungs, of bismuth in 21 samples, of gold in 72 samples, and of thallium in 6 samples.

In Tipton's second series of 24 autopsies from another (western) part of the United States (259), the findings were quite similar for the essential metals, although there were somewhat less copper and zinc in most organs, and molybdenum was largely confined to liver and kidney. Of those now considered abnormal, cadmium appeared in liver and kidney in the same concentrations as in her first series, but a large majority of other organs were lacking in this element. There was much less aluminum in all organs but lung (23 mg./Kg.) and titanium was found in only a few bodies, except for lung, where its concentration

TABLE XXXVI

CONCENTRATIONS AND CONTENTS OF "ABNORMAL" TRACE METALS WITHOUT ORGAN SPECIFICITY (WET WEIGHT) (231)

Organ	*Cr* mg./Kg.	*Cr* Total mg.	*Ni* mg./Kg.	*Ni* Total mg.	*Sn* mg./Kg.	*Sn* Total mg.	*Ag* mg./Kg.	*Ag* Total mg.
Adrenal	0.28	0.006	0.26	0.005	0.34	0.007	0.05	0.001
Aorta	0.01		0.20		0.42		0.07	
Bladder	0.42	0.08	0.23	0.06	0.19	0.04	0.07	0.01
Brain	0.36	0.76	(0.14)	0.29	(0.55)	1.16	0.04	0.08
Heart	(0.13)	0.04	(0.23)	0.07	0.36	0.11	(0.26)	0.08
Stomach & Intestine	0.18	0.36	(0.39)	0.78	0.48	0.96	(0.08)	0.16
Kidney	0.08	0.03	(0.22)	0.07	0.48	0.14	0.06	0.02
Liver	0.27	0.40	(0.32)	0.48	0.65	0.98	0.07	0.10
Lung	0.72	0.50	0.47	0.33	0.95	0.66	(0.15)	0.10
Muscle	(0.18)	5.04	(0.40)	11.2	(0.51)	14.3	(0.06)	1.68
Pancreas	0.20	0.02	(0.32)	0.03	(0.53)	0.05	(0.09)	0.008
Prostate	0.28	0.01	(0.48)	0.02	0.74	0.04	0.04	0.002
Spleen	0.63	0.13	(0.72)	0.14	(0.41)	0.08	(0.23)	0.05
Testis	0.39	0.008	(0.67)	0.01	0.22	0.004	(0.08)	0.002
Thyroid	0.42	0.01	(0.25)	0.008	1.0	0.03	0.03	0.0009
Skin, Skeleton, Adipose Tissue, Other Tissue	0.32		0.37	4.44	0.53	6.36	0.085	1.02
Sub. Total, known (mg.)		7.394		11.738		18.561		2.294
Total with estimated skin and other soft tissue at mean value ×12 Kg (mg.)		11.234		16.178		24.921		3.314
Specimens lacking metal	8		62		24		33	

Figures in parentheses indicate element missing in two or more samples.

(266). There were 4 kidneys and livers, 3 lungs, 2 spleens, and 1 aorta, heart, intestine, and muscle. In contradistinction to adult tissues, kidneys and livers and lungs contained no titanium, cadmium or tin. Aluminum was not concentrated in lung, although it occurred in amounts of 0.3-1.0 mg./Kg. in most tissues, less than that of adults. Titanium was found in only one body, in intestine, kidney and muscle. Nickel occurred in one other kidney and liver, tin was in both spleens and the sample of muscle and aorta. On the other hand, boron was in all tissues but one kidney and liver; chromium and silver were ubiquitous in adult concentrations, as was lead, but in smaller amounts than in adults. Organ specificity as determined by concentration was not found consistently.*

In the bodies of 3 older infants and children (7 weeks, 10 months and 2 years) there was no titanium. Nickel in traces was in 1 kidney; tin was found in all tissues, as was lead, while silver occurred in 7 of 12 specimens. Cadmium was present in the 10-month-old kidney (0.65 mg./Kg.) and in the 2-year-old (2.75 mg./Kg.) but not in the 7-week-old one The essential metals were found in distributions and concentrations similar to those of adults. Manganese was, if anything, more concentrated; zinc less so, while copper was comparable, showing an affinity for liver. Molybdenum was in all livers, while cobalt was present in only two.

Within the limits of these observations, and in view of what is known, the following further conclusions can be drawn; 1. Titanium, nickel, and cadmium are not essential to infant life, but accumulate with age. 2. Aluminum, chromium, silver and lead either qualify as essential trace metals, or pass through the placental membrane. Obviously titanium, nickel, cadmium, and tin do not so pass.

* Analyses of 20 stillborn infants gave essentially similar results.

was lower (2.8 mg./Kg.). Likewise lead was somewhat less frequent, being in all livers, kidneys, lungs, pancreases, bones, aortas and adrenals, but missing in a few to many samples of other tissues. Chromium and silver were also absent in one or more samples of each tissue and were found in lower concentrations, while nickel was quite uncommon. Tin, on the other hand, was widespread through most samples. There was less gallium, the same amount of bismuth and much less gold.

New elements added to the analysis were: barium, found in all samples of lung, bone, adrenal, aorta, gastrointestinal tract and thyroid, and in most samples of the other organs; cesium, in half the lungs (3.1 mg./Kg.); iron, in all tissues in high concentrations, especially spleen (280 mg./Kg.), lung (210 mg./Kg.) and liver (170 mg./Kg.); lanthanum, in a third of spleens; strontium, in every tissue (0.04-0.20 mg./Kg.) with much (20 mg./Kg.) in bone, and vanadium, in two thirds of the lungs (0.27 mg./Kg.). No antimony, arsenic, beryllium, niobium, ruthenium, thallium or zirconium were found.

One can draw some tentative conclusions on Tipton's two series, the first obtained on autopsies from New York, Memphis and Chicago, the second from a Western city. 1. Minor regional differences in exposure or accumulation of some abnormal trace metals appear, especially as regards aluminum, titanium, chromium, silver, nickel and possibly lead. 2. Molybdenum is essential only for liver and kidney. 3. Chromium and nickel are probably not essential elements. These conclusions apply only to the concentrations detectable by the method.

Trace Metals in Infant Tissues: We can gain some idea s to which metals are essential for life and which are not y examining the tissues of babies. Analyses of 2 St. Louis illbirths and 2 babies living 12 hours were revealing

Some of these metals accumulate with age in Americans, others do not. In Table XXII, Chapter V, are shown examples. Obviously cadmium, titanium, nickel and tin in all tissues, and aluminum in lung increase from little or none in infants to relatively higher concentrations at older ages. The striking examples are in cadmium and titanium.

Trace Metals in Tissues from Uncivilized People: In order to ascertain more definitely what trace metals are essential and what are not, a small number of tissues from African natives in little contact with Western Civilization were obtained by Dr. Perry from Uganda and analyzed by Dr. Tipton (266). The ages ranged from 18 months to over 50 years, there were three under 10 and four over 40. None showed any evidence of atherosclerosis in the aorta or elsewhere; even "fatty streaks" were not seen. The causes of death were several; 6 patients died of acute infections. No age trends in essential metals were apparent, as is the case with Americans. The interesting findings lay in the absence of those which might be guessed to be products of Western Civilization: cadmium (in only one kidney), nickel and tin, and the much smaller amounts of silver, lead, chromium and possibly titanium (Table XXXVII).

Conclusions: Therefore, it becomes apparent that nickel, chromium, cadmium, lead, silver and tin are not essential elements but results of civilization, a conclusion which could be drawn from the analyses of children's tissues only for cadmium, nickel and titanium. The possibility of these six elements found in American tissues being "toxic" must therefore be considered. Common sense excludes *silver* because of its low concentrations. In addition, we cannot rule out the possible essential nature of aluminium, barium, strontium, and for lung, of vanadium and ti-

TABLE XXXVII

MEAN CONCENTRATIONS OF ESSENTIAL AND NONESSENTIAL TRACE METALS IN AMERICAN AND AFRICAN TISSUES
(ANALYSES PERFORMED BY TIPTON *et al.*)
(mg./Kg. Wet Weight*)

Metal	Kidney Africa	Kidney U.S.A. 1	Kidney U.S.A. 2	Liver Africa	Liver U.S.A. 1	Liver U.S.A. 2	Lung Africa	Lung U.S.A. 1	Lung U.S.A. 2	Spleen Africa	Spleen U.S.A. 1	Spleen U.S.A. 2	American Children 0–3 Years Kidney	American Children 0–3 Years Liver	American Children 0–3 Years Lung	American Children 0–3 Years Spleen
No cases	10	24	24	3	24	24	4	23	24	4	24	22	7	7	4	5
Mn	0.39	0.43	0.36	0.57	1.13	0.76	0.49	0.58	0.19	0.27	0.52	0.13	0.55	0.98	0.45	0.400
Cu	0.26	2.76	2.9	4.47	10.6	5.7	2.8	4.49	1.4	1.7	8.67	1.3	2.89	9.0	2.9	1.9
Zn	24.5	67.2	48	65.3	68.4	48	39.5	18.3	17	33.8	22.5	21	18.4	65.0	15.2	15.9
Mo	0	0.63	0.33	0.53(1)	1.62	1.2	0	0.18(15)	0	0	0.17(17)	0	0.85(3)	0.86	0	0
Al	5.93	1.80	0.67	3.77	2.35	0.7	28.8	30.8	23	4.88	3.34	2.2	2.1	0.64	0.69	0.52
Ti	0.64(1)	0.14	0.67(5)	1.6(2)	0.26(21)	0.5(2)	3.45	7.65	2.8	0	0.31	1.0(5)	0.47(1)	0	0	0
Cr	0.037	0.09	0.04(4)	0.02	0.27	0.03(11)	0.04	0.72	0.14	0.009	0.63(23)	0.05(13)	0.30	0.22	0.97	0.31
Ni	0	0.22	0	0	0.32(13)	0.26(2)	0	0.47	0.33(8)	0	0.72(14)	0	0.17(2)	0.13(1)	0	0
Pb	Tr(4)	1.27	0.94	0.24	2.04	1.5	Tr	1.21	0.63	0.25(1)	1.33	0.38	0.17(6)	0.51	0.09	0.37
Sn	0	0.48	0.27	0	0.63	0.56	0	0.95	1.1	0	0.41(22)	0.27(19)	1.32(3)‡	1.6(3)‡	0.13(1)‡	0.33
Ag	Tr(6)	0.06	0.02	0.015	0.07	0.03	Tr	0.15(19)	0.02(19)	0.02(3)	0.23(15)	0.06(14)	0.06(5)	0.15(6)	0.03(3)	0.12
Bi	6.3(6)†	0.49(6)	1.1(6)	1.25(1)	0.61(3)	0.9(3)	0	0	0	0.25(1)	0	0.36(2)				
Cd	±2(1)	33.1	31.0	0	3.60	3.3	0	1.73(20)	1.1(11)	0	1.96(6)	1.3(1)	1.70(2)‡	0	0	0

Differences considered significant from American adults are italicized.
Numbers in parentheses indicate specimens with metal if all specimens did not show it.
Ages of the 12 African patients 3, <10 years, 1, 20–30 years; 1, 30–40 years, 5, 40–50+ years.
* *The African tissues were preserved in formalin. The per cent ash was 3 to 5 times greater than in fresh tissues (dehydration?), therefore increasing the sensitivity of the metho*
† Two patients had 18 and 19 mg./Kg. Bi in kidney, probably the result of treatment
‡ In older children only, not in babies.
1 = Tipton's first series (231): 2 = second series (239)

tanium. We can add to our list of possibly "toxic" metals bismuth and cesium.

Are these extraneous elements biologically active or inert? Could one or more of these abnormal elements displace an essential metal and thus lead to metalloenzyme inhibition or combine with sulfhydryl enzymes and so inactivate them (Table XXVIII)? If so, the possibility of inhibition causing dysfunction leading to disease is considerable.

METALS OF POSSIBLE BIOLOGICAL SIGNIFICANCE IN THE FIRST TRANSITIONAL GROUP

It is interesting that the transitional and nearby metals in the periodic table are those with most biological activity, an expression, perhaps, of their structures (267). Other than the known "essential" trace metals of the first transitional group, four might serve in metalloenzymes but have at present no known function, i.e., titanium, vanadium, chromium and nickel. Vanadium is found in all of the animal phyla, is concentrated from sea-water by tunicates as an essential oxygen carrier (268), is required by aspergillus niger (269), is concentrated in certain mushrooms (270), was probably an oxygen carrier in petroleum-forming animals, and appears in concentrations of about 1.0 mg./Kg. in all plants, dry weight (271). The case for it having a function in mammals is good. While chromium stimulates plant growth, is present in all vegetables in concentrations of 10 to 1000 γ/Kg. dry weight and is in many human tissues, evidence for its essential nature is doubtful Nickel is probably not required by mammals, although plants contain traces. The role of titanium is not known, although it is found in almost all human adult lungs. Those concentrated in certain organs may be of more significance in metabolism or in causing diseases

TABLE XXXVIII

Effect of Transitional Metal Ions on Hepatic Metabolism in the Rat*

	Ti‡	*V*	*Cr*†	*Mn*	*Fe***	*Co*	*Ni*	*Cu*	*Zn*	*Cd*
Atomic Number	22	23	24	25	26	27	28	29	30	48
Oxidation of phospholipid fatty acid	0	+	0	—	0	−50%	0			
Dehydrogenation of PFA		+								
Oxidation of double bond in PFA		+								
Oxidation of cysteine to its sulfonic acid	—	0	sl-	—		—	0			
Oxidation of thioglycolic acid	—	0	sl-	—		—	0			
Synthesis of cholesterol from acetate	0	−90%	150%	125%	−60%	−40%	0	0	0	0
Synthesis of fatty acids from acetate	0	−40%	150%	55%	−40%	0	0	0	0	0
Human liver content, American, mg./Kg.	0 26	0-Tr.	0 27	1 13	170	(0 8)	0 32	10 6	68.4	3.6
Same, African	(1 6)	0	0 02	0 57		0	0	4.47	65.3	0
Log K_1 EDTA			13[1]	13 5	14.2[2]	16 1	18 5	18.4	16.6	16.5
Ratio hydralazine binding, Cu = 1 0		0 3	0[1]	0 3	0.1[2]	0	0.2	1.0	0	0

Note: Metal binding agents CN, pyrophosphate, p-aminophenol and aminopyrine inhibited the liver enzyme of Bernheim, 8-hydroxyquinoline depressed hepatic synthesis of cholesterol and fatty acids while EDTA enhanced it (375).

PFA = phospholipid fatty acid

* From Bernheim and Bernheim (272, 274, 275) and Curran (248).

† As dichromate or chromium potassium sulfate.

** As ferric.

‡ As pertitanate

[1] As chromous.

[2] As ferrous.

turated fatty acids were oxidized very slightly. Furthermore, they showed that vanadium exhibited two effects, dehydrogenation to produce unsaturated fatty acids, and oxidation of the double bond (Table XXXVIII). The reaction was inhibited by the metal binding agents cyanide, pyrophosphate, fluoride, p-aminophenol and aminopyrine. Brain contained none of the enzyme, kidney little. When other metals were tested, manganese, and to a less extent, cobalt, were found to inhibit the system, while nickel, iron, titanium and chromium had no effect (275). Manganese, cobalt and titanium inhibited the oxidation of cysteine to its sulfonic acid. Titanium, in the form of sodium pertitanate, also inhibited hepatic oxidation of thioglycolic acid and ethyl mercaptan, but glutathione was not oxidized by this system (272).

Evidence for Vanadium Being an Essential Trace Metal: What evidence there is for vanadium being essential to mammalian metabolism is indirect but good. Aside from its use by ascidia, which use it for oxidation-reduction reactions at a time when they are buried in mud, petroleum contains varying amounts of vanadium in a porphyrin form, which has led to the hypothesis that animal organisms, and not plants, originated the formation of petroleum It is found in mammalian tissues at a fairly good concentration, said to be 0.13 per cent dry weight, 1.2 mg./Kg. for invertebrates and 0.1 mg./Kg. dry tissue for vertebrates (268). While its occurrence may be a chance contamination, universal presence and three valence states (V^{+++}, V^{++++}, V^{+++++}) with an ability to release energy similar to phosphorus make it likely that vanadium may be essential. Tipton found it only in the lung.

Vanadium is a powerful stimulant to monamine oxidase (Table XXIII) Only cobalt, of the others tested, exhibited this property to much less degree. This phenomenon

than those widespread in smaller concentrations (chromium, tin, nickel). We can supply our six rules of thumb to each.

Titanium: There is no evidence that titanium is necessary for normal function. It can, however, act as an antimetabolite. Titanium inhibits the oxidation of cysteine to its sulfonic acid (as well as thioglycolic acid) (272), but does not affect cholesterol and lipid synthesis in the rat (248). The antimetabolic action of this substance could, but does not necessarily implicate it in chronic disease. If involved, its only known effect is upon sulfur metabolism.

When a patient with moderate hypertension was treated with hydralazine in increasing doses at four-hour intervals up to 600 mg. per day, the only change in the urinary excretion of 11 trace metals was in titanium. Taking the highest value of 4 control days, this value was exceeded on 7 of 9 days of treatment; on 5 it was twice as much or more; on 2, 6 times and on 1, 50 times greater. No other trace metal so moved; the control value for vanadium anc chromium were exceeded three times, of lead twice and of manganese once of nine days. Late results of hydralazine therapy on pairs of urine specimens before and after control of hypertension showed no essential changes in mean titanium excretion. The values doubled twice and fell markedly once. There were no significant changes in the urines of 5 patients with disseminated lupus (273).

Vanadium: Bernheim and Bernheim have studied the oxidation of certain rat and guinea pig tissues as influenced by vanadium acetate or sodium metavanadate (274). They found that phospholipids were oxidized by the insoluble portion of liver proteins in the presence of vanadium; brain and liver phospholipids and soy bean lecithin were good substrates for the vanadium-enzyme system. The oxidation of many other substances were unaffected. Sa-

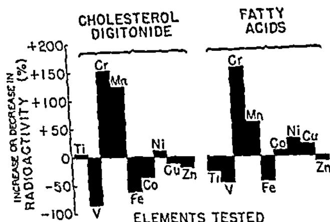


FIG 18 The effect of certain transition metal salts on the incorporation of C^{14}-carboxyl-labeled acetate into cholesterol and fatty acids by surviving rat liver (From Curran, G L.: J. Biol. Chem., 210.765, 1954)

adults, and being ubiquitous in plants and animals (256), no role for chromium is known. It markedly stimulates the hepatic synthesis of cholesterol and fatty acid in rats. No other transition element save manganese had this property (Fig. 18) (248). It did not affect decarboxylase and monamine oxidase.

Normal urine contained less than 0.05 to 1.03 γ/L. (mean <0.46), hypertensive urine less than 0.05 to 4.4 γ/L. (mean 0.88). Treatment did not change the means significantly (0.67 to 0.71 γ/L.) nor did hydralazine or EDTA cause a consistent loss.

Chromium in liver could stimulate cholesterol and fatty acid synthesis in man. There is as much, however, in infants as in adults. Only by analyzing many more tissues from primitive areas can one determine whether or not chromium can qualify as an essential metal or if not, play a part in chronic disease.

strongly suggests, but does not prove, that vanadium is an essential metallic component of monomine oxidase. Not until the enzyme is obtained pure and the metal identified can we say for certain that it is essential for amine oxidation.

The urinary output of vanadium in human beings is fairly constant, less than 0.63γ/L. (range less than 0.5 to 2.15). In hypertension, however, it was increased to three times normal values, 1.95 γ/L. (range 0.4 to 14.5). Treatment appears to bring back the values toward normal (2.86 to 0.93 γ/L.). However, only five of our values were initially greater than the highest normal.

The pharmacological effects of vanadium have been extensively studied by Jackson (276). It is an unique element in that it causes vasoconstriction in rabbits. The older literature contains equivocal reports of its effects in syphilis, tuberculosis and skin diseases; oral doses are well tolerated. In hypertensive states, giving sodium metavanadate by mouth sometimes caused transient reduction of blood pressure but also produced chills and fever. In rats, it markedly depressed fatty acid and cholesterol synthesis by liver (248) (Fig. 18).

It is possible, therefore, that vanadium deficiency, either through lowered intake or exogenous abnormal metallic competitions, is one of the causes of the conversion of intermittent vasospasm into sustained vasospasm. Consistent with this theory are: 1. Stimulation of renal monamine oxidase only by V^{+++} and V^{++++}, an enzyme which destroys norepinephrine and most other circulating vasoactive primary amines. 2. Reduction of pervanadate by hydralazine which also enhances monamine oxidase activity (277). Unfortunately, vanadium was acutely pressor for hypertensive rats, but may be depressor in dogs.

Chromium: Although found in all lungs of infants and

rier, while its absence in many adults suggests that it is not necessary after full growth.

Aluminum is almost absent from plant tissues although it represents seven to eight per cent of the earth's crust (256). Animal tissues, with the exceptions of lungs and liver, are said to contain less than plants (0.7 to 1.5 mg./Kg. in the dog, and 0.5 to 3.3 mg./Kg. in the rat) (278, 279) although a former study showed considerable amounts in human beings (brain 2.5, heart 2.1, liver 0.8, kidney 1.0 and spleen 0.7 mg./Kg.), but less than were found by Tipton *et al.* Salts have been put into baking powders, can be absorbed from cooking vessels and canning processes. A considerable amount of investigation 25 to 50 years ago indicated the lack of toxicity of aluminum, which is fed in antacid preparations to patients. The large amount found in lungs probably comes from inhaled aluminum silicate from dust. Having only one valence state, in spite of its prevalence in the earth, it has not been shown to have any essential role in human metabolism, although by our criteria, it cannot be excluded as an essential trace metal.

Scandium and gallium are found in soils. The traces of gallium in human lungs probably have been inhaled, since gallium is present in all aluminum minerals Both are relatively unreactive compounds with only one valence state.

Comment: If one were forced to choose a single trace metal to undo the harmful effects of degenerative cardiovascular diseases, vanadium would be that choice for the following reasons:

1. Vanadium stimulates monamine oxidase, thereby probably increasing the destruction of pressor, vasoactive and cerebroactive amines, and affecting hypertension thereby (Table XXIII).

Nickel: While found in all plants and animals tissues in traces, it has no known function (256). It is almost certain that this element is not essential for mammalian growth and development. There is frequent exposure in processed and manufactured foods, especially hardened vegetable oils (Chapter VII) where it is used as a catalyst (containing 0.01-2 mg./Kg.), and from corrosion of nickel vessels. No increase was noticed in human tissues after the second decade until the seventh. Therefore, although present in small amounts, we cannot state whether or not it is doing harm, although it probably has little direct action. It did not affect the enzyme systems of interest to this discussion, and is usually inert in others.

Normal concentrations in urine averaged 2.78 γ/L. with a range of less than 0.05 to 12 γ/L. Hypertensive urine contained twice as much, 5.53 γ/L. with a range of less than 0.1 to 40; only a third, however, contained more than the normal mean amount. Hydralazine caused no essential changes; treatment did not alter the mean values significantly (3.99 to 5.78 γ/L.). EDTA caused no apparent changes. Nickel cannot at the present time be implicated in cardiovascular diseases. Excessive exposure causes dermatitis or eczema.

Elements of the Third Group: There is no evidence that any of the elements in the third periodic group are essential for mammalian life. Boron, however, appears to be essential for plant life, occurring in most forms, and is necessary for reproduction (256). Only traces are found in dairy products and flesh foods, since this element is fairly rapidly excreted. In man, however, in large amounts it causes weight loss, albuminuria and gastrointestinal disturbances. Its presence in most tissues of stillborn infants means either that it is essential or that it is a contaminant in the mother easily transported across the placental bar-

18.5). After treatment the mean value diminished from 5.47 to 2.64 γ/L., five of eight values declining. Hydralazine decreased the output to about a fourth, as did EDTA. The possible role of tin is undetermined although its source lies in the products of Western Civilization, i e., tin plate, traces dissolving in some tinned foods.

Silver: Like tin, silver is widespread, occurring in every adult kidney and brain, and in almost every other sample examined (225 of 258 specimens) (231). There was no tendency for accumulation with age and almost every young tissue contained it in adult concentrations (266). It was in all urine (0.8 γ/L., range 0.23-1.4); hypertensive urine contained little more than did normal (1.4 γ/L., range 0.3-4.6). Exposure to silver is constant in our society; there is little or none in plants. Because of the small amounts found, it is doubtful that enzymatic inhibition (on copper enzymes), if present, is extensive enough to cause metabolic disorders.*

Lead: There is lead in all human tissues at birth and during life. This toxic metal accumulates, especially in bone and liver. As far as is known, it is not an essential constituent of any living organism, getting into food mainly from the use of its compounds on plants and from vessels in which food is manufactured, transported or stored. Shell fish may absorb lead from sea water contaminated with drainage from factories and animals from sprayed plants. African tissues had little.

* A knowledge of the coordination number of a *metal*, the shape of its chelate and its periodic group allows a reasonably accurate, *if indirect*, method of predicting displacement of a known essential metal and inactivation of its enzyme Conversely, by inactivation studies unknown [illegible]

2. Vanadium unsaturates fatty acids on phospholipids and oxidizes the double bond (274).

3. Vanadium depresses the synthesis of cholesterol and fatty acids (248).

4. Vanadium lessens the formation of atheromata in experimental animals (280).

If one were to choose a single abnormal trace metal as a contributing cause of hypertension, cadmium would be the choice for reasons discussed in Chapter IV.

If one were to choose three abnormal trace metals as contributing causes of atherosclerosis, chromium, cadmium and lead would be the choices. Tin could not be excluded.

METALS WITH POSSIBLE HARMFUL EFFECTS

With some certainty one can list the metals present in American human tissues which are contaminants and which may be potentially harmful, i.e., silver, cadmium, tin, antimony, arsenic, gold and lead. Of these, known toxicities are found in the cases of cadmium, arsenic, and lead; large amounts of the others are less harmful but will produce diseases or disorders. Just as in the cases of transitional metals, those which are evenly distributed throughout all tissues (tin, silver) are under less suspicion for causing disease than are those concentrated in specific organs with high metabolic activities (cadmium, lead).

Tin: There is no evidence that the metal is essential for life (256). It is not essential for plants. Little is known of its action as an anti-enzyme. It was present in almost all human adult American tissues, and in the spleens of infants; older children showed quantities comparable to those of adults. The mean normal urinary concentration was 3.22 γ/L. (range less than 0.5 to 10.0); the mean hypertensive concentration was 8.93 γ/L. (range 0.9 to

cause pulmonary fibrosis (from inhalation) (282-285), renal damage (286), this toxic metal is under considerable suspicion as a cause of chronic disease. Of all the exogenous abnormal metals found in adult American tissues, cadmium appears the most toxic. It is obviously cumulative. Supposedly 40 mg. by inhalation can cause death in man, which is strange, since the total content of adult bodies is about 120 mg. and the lethal dose in rabbits by injection is 3 mg./Kg (LD_{50}) (84). Hepatic and renal lesions are prominent features of acute poisoning in rabbits and rats; cardiac hypertrophy is universal (286). Proteinuria and renal lesions occur in exposed workers (287). There must be obvious differences between acute and chronic effects in man, especially when this metal accumulates for a lifetime. The protein in the urine is not albumin, since it appears on the heat test but is not precipitated by Esbach's reagent (287). Cadmium causes aminoaciduria in man (288).*

The source of the cadmium may lie in zinc, for it is a constant contaminant of zinc ores. There is probably one per cent or more in the galvanizing grade (Prime Western) as indicated by the following specifications adopted in 1911 by the American Society for testing materials, last

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* Cadmium causes increased excretion of the following amino acids in man exposed industrially. glycine, alanine, glutamine, tyrosine, lysine, histidine, methyl histidine All of these, except possibly lysine, can act as donors of ammonia Furthermore, serine excretion was increased 9.5 and threonine 33 times The amount of cadmium in the urine was in the same range, 12 335 μg /L. (average 20 μg /L) as we have found for hypertensive individuals (308) Cadmium was unique among four heavy metals (U, Pb, Cd, Hg) studied by Clarkson and Kench (288), who believed that it specifically inhibited the renal tubular reabsorption of these amino acids. An alternative, and to us preferable, explanation lies in the specific inhibition of decarboxylases by cadmium, thus preventing the first step of renal amino acid metabolism.

There is no toxic metal which has received such concerted attention as lead (84). It has been proposed, and discounted, as a cause of many chronic diseases, including hypertension and atherosclerosis. The predilection of American lead for adrenal, aorta, bone, kidney, liver, lung, pancreas, prostate and spleen, but not for brain, bladder, muscle and intestine, suggests that it might exert an antimetabolic function. The much smaller amounts in infantile and African tissues with a tendency to accumulate with age places it under suspicion. There are, however, no good ideas as to its effects on enzyme systems in ordinary concentrations, although lead poisoning affects the nervous system and blood. It is well known that exposure to lead in industry produces definite slow accumulation. Tetraethyl lead in gasoline is a fair source (84).

While we cannot implicate this toxic, accumulating metal in any chronic disease, in our society we cannot discount it as a possible etiological factor. Workers in lead industries, however, either develop clinical manifestation or suffer from no noteworthy disorder. The earliest symptoms of sub-clinical lead intoxication are those referable to emotional stability, being irritability, moodiness, restlessness, excitability, common complaints in this period of history. Lead salts are vasoconstrictor in perfused dogs' legs and cause vascular smooth muscle to contract (281).

Cadmium: The high renal concentrations of cadmium in American adults, its absence in infants and in African native tissues focuses suspicion on this metal as an etiological agent in chronic disease. Since cadmium can displace zinc on mercaptalbumin (243), is a highly potent inhibitor of sulfhydryl enzymes (of which Coenzyme A is an example) and at least one vitamin B_6 enzyme, can

are no good examples) we could expect on the basis of mass alone the following enzymatic inhibitions: Renal, 55 per cent; hepatic, 6 per cent; pancreas, 5 per cent; thyroid, 5 per cent; adrenal, 8 per cent; aorta, 5 per cent; intestine, 5 per cent; brain, 0 per cent. Obviously a 5 per cent reduction of metabolic activity would probably be unmeasurable, while a 50 per cent would manifest itself in disorder which could lead to disease.

Renal decarboxylase is inhibited *in vitro* at a lower concentration of cadmium than that present in adult kidney. Other enzymes known to be inhibited *in vitro* are leucine aminopeptidase, carnosinase, succinic dehydrogenase, choline oxidase (Table XXXVIII), possibly through sulfhydryl binding. If other metalloenzymes are specifically inhibited, such as vitamin B_6 enzymes, it is obvious that effects of low concentrations could be profound and in the case of vitamin B_6, result in a conditioned, local deficiency.

As in the case of zinc and lead, cadmium can be dissolved in slightly acidic media. Therefore, foods and waters coming in contact with cadmium could become contaminated by traces. There are three possible sources: 1) Water is usually piped in American houses through galvanized zinc coated iron pipes. If soft, aerated in muncipal water stations to contain carbon dioxide and chlorinated, appreciable quantities of zinc, lead, and presumably cadmium could be dissolved from the galvanized coat. If hard, however, insoluble carbonates are laid down on the coating, protecting it from solution and corrosion. Water softeners probably would not soften water enough to corrode zinc. Chlorinated water, even when hard, takes up zinc.* 2) Carbonated beverages are acidic and will take up zinc, lead, and presumably cadmium from galvanized or zinc-lined

* A probable source of abnormal trace metals in some soft and acid water areas is in the corrosion of hot-water heaters.

revised in 1949. The maximum impurities allowable are (per cent):

	Lead	Iron	Cadmium	Total Not Over
Special High Grade*	0.006	0.005	0.004	0.010
High Grade*	0.07	0.02	0.07	0.10
Intermediate	0.20	0.03	0.50	0.50
Brass Special*	0.60	0.03	0.50	1.00
Selected*	0.80	0.04	0.75	1.25
Prime Western	1.60	0.08	—	—

* *It shall be free from aluminum.*

Since Prime Western zinc is the grade used largely in galvanizing and no limits for cadmium are provided, it is therefore probable that zinc coating, so widely used in pipes and food processing, and brass are likely sources of the cadmium found to accumulate in human tissues.

Cadmium poisoning has been reported in human beings drinking acid beverages made in cadmium plated (yellow tinged) ice trays (289).

The high concentrations in adult human kidneys (33.1 mg./Kg. or about 10 mg. of the metal) with secondary affinities for liver, pancreas and thyroid, and lesser amounts (±1 mg./Kg.) in adrenal, aorta, stomach and intestines, suggests that antimetabolic activity could be exerted especially in those organs of greatest import to essential functions. Its absence in most hearts, muscle tissue, spleens, and all brains is interesting, indicating that proteins or enzymes in those areas do not chelate or bind this metal readily, for cadmium is readily chelated by sulfur and nitrogen ligands (its affinity for EDTA, for example, exceeds that of zinc, cobalt, ferrous iron and manganese). Its affinity for zinc suggests that it might interfere with zinc enzymes, displacing the essential metal as it does on serum albumin (by displacement from indole groups). If zinc enzymes were inhibited by cadmium (although there

that zinc poisoning, which does not occur in animals fed small amounts, may be actually caused by contaminating cadmium.

The source of cadmium, which does not occur in plants, is obviously in the products of Western Civilization.*

Other Metals: Analyses for other commonly occurring possibly toxic metals, such as arsenic, antimony and bismuth of group V A have revealed no striking accumulations in human tissues. There may be as much as 0.3 parts per million of arsenic in man, much of it in hair and nails, derived from fish and sea-foods, or from contaminants of food. Arsenic displaces phosphorus in essential phosphate mechanisms, but the amounts are probably too small to cause functional disorders, and habituation or tolerance develops. Antimony can gain access to foods from enamels, solders, tin-foil, rubber, and insecticides. The "normal" amounts in human tissues are not known, but presumably it also displaces phosphorus. Bismuth was found by Tipton in only a few bodies in small amounts in liver and kidneys (12 of 48 cases), and is probably not to be considered of universal import. Mercury appeared in a surprisingly large number of kidneys analyzed by Griffith *et al.* from patients with congestive heart failure who had supposedly never received diuretics containing this metal (260).

Cardiovascular Implications: Aluminum and strontium were present in all samples of American heart muscle. These metals, plus lead and tin, were found in all aortas. In kidney there was the additional metal cadmium; in liver, these five and silver. In adrenals were the same six and

* Preliminary single analyses of five bottled drinks revealed a carbonated water, 21, a popular carbonated drink, 11; a citrous drink, 1; a grape juice, 1.5, a whiskey, 5.5; in parts per billion. Three of these values are considerably higher than those of normal urine. The grape juice contained relatively much nickel, tin and lead.

containers in which they are piped, prepared or bottled. Lemonade made in galvanized pails has *produced acute gastroenteritis.* The widespread use of carbonated acidic drinks ("pop") in this country is a possible source which has not been explored. 3) Acidic foods prepared in zinc-lined containers, especially vegetables, can absorb cadmium and lead.

According to Monier-Williams (256) zinc is taken up by the following ingested products; presumably cadmium is also dissolved: Chlorides in water, *chlorinated water,* carbonated water, oxygenated water (from brass), soft acid water (from brass), milk (during pasteurization), milk (from bottle caps), alcoholic, acid or saline liquids, especially wine, vinegar, soup, orangeade, lemonade, beer, molasses (from zinc coated vessels in sugar refineries), maple sugar, honey, chocolate and candy (*wrapped in zinc foil*), gelatin (from zinc coated vessels and wire netting on which *it is dried*), *dried fruit* (from drying trays), jam (from pans). Poisoning resembling that from cadmium has been reported from soda water, rain water (collected from galvanized roofs or stored in tanks), stewed apples (from galvanized iron vessels), root beer, cider. *Coffee is floated* and dried on galvanized trays. All galvanized iron vessels are suspects, since electrolytic action between the iron and the zinc may be initiated by moist foods.

Cadmium is widely used for washing machines, electric cooker parts and refrigerator trays. *It is* absorbed by weakly acidic foods, sugars (jam), wine, tomatoes, fruit, fruit juice, ice cubes (from acidic water?), coffee, cooked food, gelatin; and attacked by lactic, succinic, citric and tartaric acids. Possible sources of contamination; *besides* galvanized zinc and cadmium plated vessels, are solders, fruit insecticides. The similarity of known sources of acute poisoning and those of zinc are remarkable, and suggest

presence in large quantities and its lower affinity for some proteins than other metals with a higher EDTA-metal stability constant. Of course, excessive quantities of metals obey the law of mass action and can be partly removed; minor quantities cannot until better chelators are developed for fairly specific purposes.

What good will it do our patients if these abnormal metals are removed from their bodies? We do not know. The subject of metals and chronic diseases is barely beginning to be appreciated. Forbes *et al.* say, for example, "It is conceivable that the continuous ingestion of infinitesimal amounts of these metallic elements present in natural foods, leading to their very gradual accumulation in the tissues, may contribute to the processes of senescence in proportion to the degree with which they are combined with tissue proteins (apoenzymes) and the extent to which they inhibit or distort enzyme action in such combinations" (290). While this may be true, it is more likely that many of the diseases common only to our Civilization may be caused by the nonessential metals contaminating our foods, as a result of our industrial habits. We may be pleasantly surprised at the therapeutic results of their removal. Scleroderma has already been completely relieved in at least one instance by EDTA (291).

A logical therapeutic regimen within the limits of present-day vision is a concerted effort at removal by relatively nonspecific chelators followed by replacement of essential metals so removed. Generalized deficiency states of the essential metals, iron, cobalt, copper and molybdenum is probably unlikely under such a regimen; manganese and zinc may require replacement. Too much of an essential metal, however, probably can cause as much disorder as too little. When deficiencies are recognized, they can be treated.

Local deficiency states caused by abnormal metal com-

boron, chromium, gold and nickel. Barium was found in all aortas. Cardiovascular organs, except the heart, appear to have the ability of accumulating at least four abnormal metals. Several are known antimetabolites for man or living organisms (Table XXXII).

Many of these metals are found in normal and hypertensive urine (308-310), cadmium and manganese being increased in the latter. Specific enzyme inhibition has been demonstrated for several, which may play a part in cardiovascular (311) and other chronic diseases (312).

CLINICAL IMPLICATIONS

At the present time, there are no known methods for removing from the human body one or more of these abnormal metals and leaving the essential ones. Furthermore, the rules of chelation make such a procedure inconceivable. Each metal probably has a different stability constant for different proteins and removal therefrom would require toxic amounts of very strong chelators which would complex or bind such essential metals as iron and magnesium. The situation may be roughly analogous to that in argyria, where silver is permanently deposited in the skin and cannot be removed by any known method.

On the other hand, certain metals might be eliminated from the body by the judicious use of chelators with specialized groups. Thus, aurintricarboxylic acid fairly selectively binds beryllium in a soluble lake, reversing some of the actions of beryllium poisoning (232). A sulfur-containing chelator might sequester cadmium, although the affinity of this metal for renal tissue is high, BAL giving up cadmium to kidney which it has displaced from other areas. While such oxygen-nitrogen containing chelators as EDTA and its relatives prefer copper and nickel to other elements in the first transitional group, in actual practice zinc is largely removed, probably because of its

Chapter VII

SOME MECHANISMS IN ATHEROSCLEROSIS

INTRODUCTION

ALTHOUGH atherosclerosis is usually a disease of Western Civilization, it has been observed in nomads. To begin to understand its pathogenesis, one must consider the influences which civilization may contribute and those which can lead to the disease in "uncivilized" people. A brief discussion in a monograph on hypertension is justifiable, for hypertensive patients are prone to develop the disease, treated hypertensive patients die mainly of its effects (319), hypertension accelerates its progress and there may be some basic factor common to both.

Atherosclerosis can occur without diastolic hypertension. Severe degrees of the disease in the aorta causing loss of elasticity produce systolic hypertension because the "pipes are hard," but do not of themselves cause elevated diastolic pressure. Contrariwise, hypertension can persist without significant atherosclerosis, especially in China (8, 313, 440).

In 1941 Snapper made some pertinent comments which are lately being appreciated (8). "Another point which must be specially mentioned is the infrequency of arteriosclerosis in North China. The rarity of arteriosclerosis is proved by the scores of middle-aged patients dying from all sorts of diseases showing hardly any sclerosis at autopsy. Extensive arteriosclerosis certainly does occur in North China but the thickened inelastic aorta with the widely

petition with metalloenzymes pose a more difficult problem of replacement, especially when the abnormal metal is more firmly complexed to enzyme than is the essential one. If a vitamin coenzyme is involved in the metalloprotein complex, it need be also replaced. Local enzymatic deficiencies have been postulated; for example, in the case of vitamin B_6 deficiency in the skin causing seborrheic dermatitis (292).

We may speculate on the results of such a therapeutic trial aimed at restoration of normal metallic balances. If the copper involved in the formation of melanin were partly displaced by an exogenous abnormal metal deposited in the skin, or were removed therefrom, the resultant grey hair and deficient tanning could be reverted to normal by removal of the offending metal and replacement of the copper. If the excessive cadmium, nickel, lead or titanium could be removed from human tissues, the part that one or more of these metals might play in hypertension, atherosclerosis, malignant tumors, arthritis, collagen diseases or allergic responses might be mitigated; none of these conditions can be excluded as not being influenced by abnormal trace metals. The field is wide and the frontier untrod.

Perhaps some day, when these hypotheses are more firmly proven and specific metals strongly implicated in the causation of diseases, industry will prevent contact of foods with those metals shown to accumulate in American tissues, such as nickel, cadmium, tin and lead. The subject would then enter the field of preventive medicine, rather than that of therapeutics, where it now lies.

PATHOGENETIC FACTORS

According to Friedman *et al.* (314) the following schema invokes the multiple etiological factors and illustrates the pathogenesis of atherosclerosis:

Time	×	Intrinsic (?) Intimal Derangement	×	Quantitative and Qualitative Alteration of Plasma Lipids Including Cholesterol	×	Blood Pressure	= Atherosclerosis

We will consider each of these factors separately.

1. Blood Pressure: Rarely does long-standing diastolic hypertension in Caucasians exist beyond the age of 40 without atherosclerotic lesions being found in aorta, major arteries or coronaries. Experimental hypertension is necessary to induce atherosclerosis in the rat, a resistant animal, and is desirable in the dog. Fat in serum can be made to infiltrate the walls of arteries under high pressure, especially if the intima is injured (315). Even in normotensive persons, lesions develop at the sites of changes of pressure, such as the mouths of the renal arteries, in the Circle of Willis and at the bifurcation of the aorta (316, 317). Atherosclerotic gangrene seldom occurs in the arm but is frequent in the leg, where the hydrostatic pressure of the blood in the upright position is added to the blood pressure (318). These lesions are believed to be the result of pressure causing deposition of insoluble cholesterol or its esters subintimally either by forcing them into the vessel walls or preventing their diffusion out after entrance via the vaso vasorum.

2. Intimal Injury: Mechanical injury to the intima of dogs results in the formation of atheromata (320-322). It is difficult to understand how injury can occur at a normal pressure, although acute hypertension in animals (323)

ulcerated intima, so frequently found in autopsies in the Western part of the world, is decidely rare here. This explains why the genuine angina pectoris syndrome, and also the picture of coronary thrombosis with myocardial infarction are only rarely encountered. During the past two years we saw three possible cases of this disease in the combined material of the common and private wards, the outpatient department, and the very busy emergency clinic of the hospital, although in every doubtful case repeated electrocardiograms with four leads are taken and scrutinized with utmost care. However in December 1940 one classical example of coronary thrombosis with typical findings at the autopsy was observed. The rarity of coronary thrombosis in North China is the more striking because the increase of the frequency of this affection in America and Europe is appalling. Even in diabetes mellitus extensive arteriosclerosis must be infrequent in North China because diabetic gangrene is as rare here as senile gangrene.

"It is difficult to give an explanation of this characteristic feature of geographic pathology. One can, of course, fall back on the equanimity of the Chinese, but the differences in nutrition of Chinese and Westerners may give a better explanation. Arteriosclerosis begins as a fatty infiltration of the intima of the vessel walls. Quantitative and qualitative differences exist between the lipoid content of the Chinese and the foreign diets as has been mentioned before. The Chinese diet contains only small amounts of cholesterol but considerable quantities of unsaturated acids, especially of linoleic and linolenic acid. It is certain that the average cholesterol content of the blood of the Chinese is lower than that of Westerners and this gives perhaps an indication why the tendency to lipoid infiltration of the vessel wall is so much smaller among the Chinese."

metal interference (with decarboxylases, for example); that in liver by marginal concentration of vitamin B_6, excessive saturated fatty acid load and possibly metals There is no evidence for a generalized deficiency state except for the high incidence of dandruff in the population, believed by some to be dependent upon vitamin B_6 and fatty acid imbalance.

3. Trace Metals: The synthesis of cholesterol and fatty acids by surviving rat liver can be influenced by metals of the first transitional group (Fig. 18). Chromium and manganese have a pronounced enhancing action, vanadium a depressant one (248). Vanadium also promotes unsaturation of phospholipid fatty acid and oxidation of the double bond, opposed by manganese (Table XXXVIII). There is no evidence, however, that chromium is implicated in the hypertensive process. In American tissues, hepatic chromium is much less concentrated than manganese, a known lipotropic agent (231, 259) (Chapter VI). Many metals directly affect oxidation of unsaturated fatty acids *in vitro*. Hydrogenation, to harden or saturate them, is accomplished commercially mainly by copper and nickel; sizeable quantities enter the fat during processing (256). Cadmium, however, inhibits at least one vitamin B_6 enzyme, DOPA decarboxylase, (Chapter V) although it does not affect hepatic synthesis of cholesterol in the rat (331). Obviously, we need to know much more about the effects of abnormal metals on the enzymes concerned in fatty acid and steroid synthesis.

A significant series of experiments were done by Curran and Costello in rabbits (280). Hypercholesterolemia was induced by feeding cholesterol at the 3 per cent level for 4 weeks. On resumption of a normal diet, cholesterol levels usually fall slowly. Half the rabbits were fed vanadium as $VOSO_4$ (0.05 per cent) for 6 weeks. There were

and chronic hypertension in man will result in deposition of lipid in the high pressure areas. This process is hastened if lipid in blood is elevated (324).

Subintimal "injury" from biochemical alterations in the mucopolysaccharides of collagenous tissue results from pyridoxine deficiency in the monkey (325, 326). The changes found resemble the earliest lesions of atherosclerosis (327-330).* It is possible, therefore, that a conditioned vitamin B_6 deficiency not only affects the enzymes concerned in protein metabolism resulting in hypertension (Chapter V) but also initiates the arterial lesions in which cholesterol is deposited.

It should be emphasized that the vitamin B_6 deficiency postulated in this discussion is a local, conditioned deficiency state and not a generalized one, and that it involves enzyme systems in kidney and liver but not necessarily in brain, blood forming organs or skin. The complex Schiff base of pyridoxal and amino acids is a strong chelating agent, for example, and could form a stable chelate with several abnormal metals. *Generalized* deficiency of vitamin B_6 is accompanied by low blood pressure and skin manifestations similar to seborrheic dermatitis and ariboflavinosis. A *local* deficiency in kidney could be induced by marginal concentrations of vitamin B_6 and especially trace

* Rinehart and Greenberg state: "Arteriosclerotic lesions develop regularly in the rhesus monkey subjected to prolonged pyridoxine deficiency. The initial lesion is characterized by the accumulation of a mucinous substance in the intima and, to a less extent, in the media of the arteries involved. This material exhibits the metachromatic staining property characteristic of mucopolysaccharides. Associated with the accumulation of this substance, cellular proliferation occurs and collagenous and elastic tissue fibers are formed. Studies of human arteriosclerosis indicate that basically similar sequences are seen in the evolution of the human disease. The morphologic features of the experimental vascular lesions and those occurring in man are similar. The possible role of pyridoxine deficiency in the etiology of human arteriosclerosis remains to be determined" (325).

examine the possibilities, we can look at factors of suspicious import in hypertension which could conceivably influence the development of cholesterol-containing atherosclerotic plaques in arteries.

There is no good evidence that the blood cholesterol is higher in American hypertensive than in normotensive people. Therefore, the increase in the rate of progression of atherosclerosis in hypertension is probably largely due to intravascular filtration pressure causing deposition of lipids through the intima (319).

Hypertension and atherosclerosis, however, may be interrelated in a more fundamental fashion than by mechanical excessive filtration of cholesterol through intima by the high pressure, when there are adequate cholesterol levels in blood. 1) A conditioned vitamin B_6 deficiency may involve both disorders; 2) abnormal trace metals may not only affect the hypertensive process but increase cholestrol synthesis. At this point the reader may wonder whether or not the author has an obsession with vitamin B_6 and its functions. Upon careful thinking in terms of enzymatic mechanisms, this coenzyme continually obtrudes itself into possible schemata derived from experimental and clinical data, both in hypertension and in fatty acid metabolism.

We must turn to epidemiologic data for evidence that there *is no* common denominator of these two diseases. Some atherosclerosis but no hypertension has been found in Alaskan Esquimaux (332); the incidence may be smaller than in whites. Hypertension is extremely common in Hawaiian sugar plantation workers, as is atherosclerosis, but severe coronary sclerosis is less frequent than in Caucasians (333). Atherosclerosis is said to be prevalent in Kirghiz nomads, as is contracted kidney (from hypertension?) (334). Snapper observed hypertension but little

no significant differences in hepatic cholesterol at the end of this time, but aortic and serum cholesterol values were about half the controls in the animals receiving vanadium. Likewise the livers of these rabbits incorporated C^{14}-labeled acetate into cholesterol at a markedly reduced rate. Thus, both endogenous synthesis and aortic deposition of cholesterol were depressed considerably by vanadium.

Therefore, vanadium, as a possible essential metal, manganese as a known one and chromium as an abnormal one can be implicated in cholesterol metabolism. As will be considered below, any metal interfering with renal enzymatic mechanisms also cannot be excluded as an indirect participant in vascular damage, initiating deposition of lipid in arteries.

SOME COMMON DENOMINATORS OF HYPERTENSION AND ATHEROSCLEROSIS

One anatomical common denominator between the two diseases lies in the location of the lesions. When involving the renal arteries or their mouths, reduced renal blood flow may result in diastolic hypertension of sufficient degree to restore flow to normal (Chapter IV). These lesions have been demonstrated frequently in hypertensive patients and confirmed by physiologic measurements. It is also possible that chronic hypertension may influence deposition of lesions in the smaller renal vascular areas which of themselves cause further hypertension on a renal ischemic basis. Thus will one vascular disease worsen another in a vicious circle.

There may be chemical common denominators which predispose human beings to both hypertension and atherosclerosis. This is no new idea, for many people have wondered about the relationship. The geographic and racial distributions of the two are often quite similar. To

is probable that local deficiency of vitamin B_6 due to the interference of its trace metal by an extraneous one could probably have the same result. The intimal injury in vitamin B_6 deficient monkeys is exactly like the earliest lesions of atherosclerosis.

Comment: Some derangement common to both diseases may be present but atherosclerosis, with which the American public is riddled, is more frequent in the population than is hypertension. Therefore, while atherosclerosis can and does occur without hypertension, the contrary is unusual in our civilization but frequent in others. Both abnormal trace metals and local pyridoxal deficiency may be implicated.

THE ROLE OF FAT AND OTHER LIPIDS

Let us review modern ideas on the pathogenesis of the lesions other than the factors already discussed. Most of the recent interest in the subject has centered on fats. Quite a case can be made for the role of cholesterol, which is largely carried by lipoproteins, as a strong link in the chain of *reactions* leading to the formation of plaques; the subject has had its ups and downs since 1914, but probably is here to stay. As Aschoff so aptly put it: "From plasma of low cholesterol content no deposition of lipoids will occur even though the mechanical conditions are favorable" (327).

Normal Cholesterol Levels in Blood: What is the normal level of blood cholesterol? That is a difficult question to answer. The levels found in Europeans and especially Americans may not represent "normal" values, but rather average values in a population subject to the disease. If so, we should look elsewhere at healthy adults to determine our normal standards and thus our therapeutic aims in controlling and reversing the atherogenic tendencies of

atherosclerosis in poorer Chinese (8); sometimes the condition was malignant. Therefore, while the two diseases usually are found together in the same population, exceptions in both directions may exist. Coronary sclerosis, however, is much more common in hypertensive than in normotensive people (335). Coronary sclerosis may be a different disease than aortic atherosclerosis, or may be a different manifestation influenced by local cardiac factors. Likewise cerebral atherosclerosis may differ. Undoubtedly, however, the underlying biochemical alterations are a common denominator. The epidemiological data does not prove the lack of association of the atherosclerosis seen in hypertensive states in Western countries, but merely indicates that each condition can, in some areas of the world, exist separately.

Experimental evidence, however, which points to a close association between the kidney and atherosclerosis is accumulating. Holman was the first to show that arteritis appeared in dogs fed butter only when the kidneys were damaged by uranium or mercury (336). Methods for producing experimental atherosclerosis have been developed which fit into Friedman's schema, if "kidney" is substituted for blood pressure. Renal damage will produce atherosclerosis in rats and rabbits fed cholesterol (331, 332). Nephrectomy causes an increase in plasma cholesterol and low density lipoproteins, especially when protein is fed (385). Unfortunately, we have been unable to cause the disease by feeding rats and chicks stearate and any one of eleven metals.

One further factor which may be common to the two disorders is in pyridoxal deficiency. Olsen and Martindale were able to produce chronic hypertension in young rats by desoxypyridoxine, an antimetabolite for vitamin B_6 (194). While theirs was a generalized deficiency state, it

the populations with high values. Just because a disease is common does not make it, or any one of its measurable parameters, "normal."

Considerable information comes from studies in other than Western countries (Table XXXIX). If these values for blood cholesterol be correct, as there is little reason to doubt, the "normal" range is 120 to 160 mg. per cent; higher values may be ascribed to dietary influences or their concomitants. That environment and an increasing "standard of living" may affect blood lipids was well shown by Toor *et al.* in their study of recent immigrants to Israel compared to immigrants living 20 years or more in that country (338) (Table XL).

In Table XLI are shown some wide variations in total cholesterol and other lipids in blood, done by analytic methods which are considered quite accurate, from various Western countries. The variations are unexplained. Page *et al* tried to check the differences between their analyses done in New York (339) and Boyd's done in Ontario (340); they state, "our results for cholesterol determined in the presence of the other lipids are likely to be low rather than high. For the fact that our normal cholesterol values range so much higher than those of Boyd (in Ontario) and of Gardner and Gainsborough (in England), we therefore lack an explanation. We can find no source of error for our results and none is obvious for theirs." Since Boyd's normal subjects were taking the standard high fat diet customary in this country (340), it is possible that an environmental factor not present in England and Ontario but influencing levels in New York was operating.

Effect of Blood Levels of Total Cholesterol: Most investigators believe that coronary atherosclerosis does not occur to any appreciable extent when blood cholesterol is low. Furthermore, some reversal of atheromata is in-

TABLE XXXIX

Some Blood Cholesterol Levels in Healthy Male Subjects

Location	*Race*	*Mean Age*	*Mean mg. %*	*Dietary Fat %*	*Method*	*Author*
Calcutta	Hindu & Mohammedan*	—	140	—	Myers & Wardell (Whole blood)	Bose & De (1936) (378)
Calcutta	Indian	—	116	—	(Whole blood)	Boyd & Ray (1928) (379)
	Indian	—	140	—	(Whole blood)	Ghose (1933) (380)
E. Arctic	Esquimo	—	141	High	(Bloor)	Corcoran & Rabinowitch (1937) (381)
Alaska	Esquimo	—	203	35	(Bloor)	Rodahl (1954) (332)
S Africa	Bechuana	21–38	149	<20	(Lieberman-Burchard)	Walker & Arvidsson (1954) (382)
	Basuto	21–40	153	<20		
	Bantu	21–40	167	<20		
	Bantu, Westernized	21–40	178	20–25		
	Europeans	21–30	206	30–35		
	Europeans	41–50	238	30–35	(Lieberman-Burchard)	Keys *et al.* (1954) (383)
Spain	Laborers	45	210	27		
	Professional	45	254	40?		
Naples		45	231	20		
London		45	252	35		
Minnesota		45	247	40		
Israel	Yemenites	45–54	160	—	(Bloor)	Toor *et al.* (1954) (338)
New York		20–91	232	—	—	Page *et al.* (1935) (339)

Note: In another survey, Bronte-Stewart *et al.* showed that in the Cape Peninsula, Africa, cholesterol values done by the same method were: Bantu, 166.3 ± 47.2; Cape Colored, 204.1 ± 54 8 and European, 234 0 ± 52 9 mg. per 100 ml. serum (440)

* Twenty-four women, 76 men.

TABLE XLI

VARIATIONS OF PLASMA CHOLESTEROL LEVELS IN WESTERN COUNTRIES*

Author	*Location*	*Date*	*Total*	*Free*	*Phospholipids*
Gardner and Gainsborough	England	1927	153 ♀ 169 ♂	54 50	
Man and Peters	Connecticut	1933	207♂		222
Boyd	Ontario	1935	177♂	52	185
Page, *et al.*	New York	1935	232♂	82	181
Peters and Man	Connecticut	1943	194	54	240
Gertler and Garn	New York	1950	224		299
Gubner and Ungerleider	New York	1949	211		
Keys	Minnesota	1949	218		
Kornerup	Denmark	1950	203	55	172
Block, *et al.*	Minnesota	1951	181		234
Perry and Schroeder (Hypertensive)	St. Louis	1955	226		

NOTE: The earlier determinations were done by digitonide precipitation and the later usually by acetic anhydride which tends to give lower values (439).

* From Page, *et al.* (339) and Katz and Stamler (356).

TABLE XL

COMPARISON OF SERUM LIPIDS, CHOLESTEROL AND LIPID-PHOSPHORUS IN THE OLD AND NEW YEMENITE IMMIGRANTS IN ISRAEL*

Age Group	Total Lipids mg %		Relative Difference %	Total cholesterol mg. %		Relative Difference %	Lipid-phosphorus mg. %		Relative Difference %
	Old Immig.	New Immig		Old Immig.	New Immig		Old Immig.	New Immig.	
				Men					
35–44	639	558	11	188	146	28	9.3	8.4	10.0
45–54	695	602	15	195	160	22	9.6	8.9	7.8
55–64	654	603	8	191	158	20	10.4	9.5	9.8
				Women					
35–44	688	620	11	196	172	14	9.8	9.8	0
45–54	731	607	20	213	170	22	10.6	8.7	21.0
55–64	732	615	19	220	205	7	10.9	10.3	0.3

For the purpose of this Table, values of the new immigrants' group were considered as 100%. New Immigrants = living in Israel 3 to 5 years. Old immigrants = living in Israel over 20 years

* After Toor, Agmon and Allalouf (338).

acid esters of cholesterol, regardless of the length of the carbon chain, melt at higher than body temperatures, the lowest is for oleate (44.5°C.) and linoleate (42°C.); compare stearate (82.5°C.) and palmitate (90°C.) (348). Therefore variations in solubility and melting point may determine deposition of these esters in the lesions. Solubilities of the cholesterol esters of β-lipoproteins, believed to be of atherogenic importance (350), are not known.

Since pyridoxal is concerned with hepatic desaturation of di- and tri-unsaturated fatty acids to tetra- and hexa-forms (349), this coenzyme could influence the type of ester. Experiments in our laboratories, however, have failed to show that vitamin B_6 raises the iodine number of plasma lipids when given for a week or 10 days; the tendency was for it to fall (Table XLII). Surprisingly enough, the iodine numbers of blood lipids was found to be much higher in Chinese (8) than in American patients (Table XLIII), probably a reflection of their high unsaturated fatty acid diets.

Other Lipid Substances: We have not considered the phospholipids of plasma, nor the chylomicrons containing neutral fat, nor the lipoprotein fractions which carry cholesterol. These are complicating parameters whose significance is unclear. Their relations are shown in Table XLIV. Keys has said: "At the present time (1951), it is entirely unjustified to attribute to G measurements any special virtues beyond that for simple cholesterol measurements for the prediction of atherosclerosis or the estimation of the activity of the atherosclerotic process" (351). The type of lipoprotein, its solubility and its physical characteristics, however, may have atherogenic properties. These large molecules transport lipids and steroids in blood (352). Therefore, an increase in β-lipoproteins may do something to the process, directly or indirectly, but at

ferred in patients dying of debilitating diseases (341) with depressed blood lipids. In the monkey, both vitamin B_6 deficiency and elevated blood cholesterol are necessary to induce atheromata; levels are higher in deficient than in normal monkeys fed cholesterol (324). Since not only cholesterol, but other suspended particles, will filter through intact intima (342, 343), the blood level is the obvious factor in determining whether or not this sterol is deposited in the lesions. There is no evidence at present, however, to implicate vitamin B_6 in the synthesis of cholesterol.

The deposits in the aortic plaques are mainly esterified cholesterol (316, 344-347). Schoenheimer found that there was a steady increase with age of both free and cholesterol ester extractable from the aorta as atherosclerosis developed. The proportion of free cholesterol to bound cholesterol, however, was relatively constant (22.5 to 31.9 per cent) showing no age trend, while cholesterol ester calculated as oleate tripled at older ages with advanced lesions. In other words, although the aortas contained more extractable fat, the cholesterol esters in atheromatous aortas were relatively greatly increased. Most of the esters were oleate, palmitate and stearate, with small amounts of unidentified unsaturated fatty acid esters. There was also a marked increase in aortic phosphorus and lecithin with atheromata and a decrease in free hexosamine (433).

The Nature of Cholesterol Esters: Cholesterol is a very insoluble substance; how all of it is transported in blood is not known, but most is carried by lipoproteins. Esters of stearate, palmitate and oleate are found in human blood and tissues (348). Cholesterol linoleate is considerably more soluble and linolenate much more soluble than is the stearate ester. Solubility in tissues and tissue fluids may be of considerable importance. Although all fatty

acid esters of cholesterol, regardless of the length of the carbon chain, melt at higher than body temperatures, the lowest is for oleate (44.5°C.) and linoleate (42°C.); compare stearate (82.5°C.) and palmitate (90°C.) (348). Therefore variations in solubility and melting point may determine deposition of these esters in the lesions. Solubilities of the cholesterol esters of β-lipoproteins, believed to be of atherogenic importance (350), are not known.

Since pyridoxal is concerned with hepatic desaturation of di- and tri-unsaturated fatty acids to tetra- and hexa-forms (349), this coenzyme could influence the type of ester. Experiments in our laboratories, however, have failed to show that vitamin B_6 raises the iodine number of plasma lipids when given for a week or 10 days; the tendency was for it to fall (Table XLII). Surprisingly enough, the iodine numbers of blood lipids was found to be much higher in Chinese (8) than in American patients (Table XLIII), probably a reflection of their high unsaturated fatty acid diets.

Other Lipid Substances: We have not considered the *phospholipids of plasma, nor the chylomicrons containing* neutral fat, nor the lipoprotein fractions which carry cholesterol. These are complicating parameters whose significance is unclear. Their relations are shown in Table XLIV. Keys has said: "At the present time (1951), it is entirely unjustified to attribute to G measurements any special virtues beyond that for simple cholesterol measurements for the prediction of atherosclerosis or the estimation of the activity of the atherosclerotic process" (351). The type of lipoprotein, its solubility and its physical characteristics, however, may have atherogenic properties. These large molecules transport lipids and steroids in blood (352). Therefore, an increase in β-lipoproteins may do something to the process, directly or indirectly, but at

TABLE XLII

IODINE NUMBER OF SERUM LIPIDS BEFORE AND AFTER ORAL B_6*

Patient	*Age*	*Sex*	*Iodine Number*		*Total Dose mg*	*Diagnosis*
			Before Vitamin B_6	*After Vitamin B_6*		
T. C.	77	♂	87			
			100	58	250	Myocardial infarction; Parkinsonism; atherosclerosis
G. E.	76	♂	54	45	300	Myeloid leukemia; aortic stenosis; atherosclerosis
C. H.	61	♂	60	56	250	Metastatic carcinoma; atherosclerosis
B. H.	53	♀	53	59	150	Metastatic fibrosarcoma
L. J.	58	♂	83	70	300	Myocardial infarction; atherosclerosis
R. LeG.	19	♀	42	37	250	Fracture spine, accident
M. R.	68	♀	59	69	250	Atherosclerosis; diabetes, mild
G. S	74	♂	33	67	250	Atherosclerosis, carcinoma of prostate
G. B.	58	♂	78	89	150	Hypertension; atherosclerosis
T. B.	74	♀	126	77	350	Metastatic carcinoma of breast; atherosclerosis
M. J.	50	♂	124	71	350	Pulmonary insufficiency and fibrosis; atherosclerosis
E. K.	64	♀	71	34	350	Atherosclerosis, lobar pneumonia, convalescent
F. S.	55	♂	62	58	300	Atherosclerosis; hypertension
Mean	61		74	61		
S.D.			27.6	15.0		

From data of Perry, Schwartz, Hager and Schroeder.
* Fifty mg. pyridoxal HCl per day.

TABLE XLIII

IODINE NUMBERS OF SERUM LIPIDS, WHITE PATIENTS

Patient	*Age*	*Sex*	*Total Cholesterol mg / 100 ml.*	*I_2 No.*	*Atherosclerosis Diagnosed*	
E. K.	64	♀	96	71	+	Lobar pneumonia, convalescent
P. M.	65	♂	101	94	+	Pulmonary insufficiency, bronchiectasis
F. F.	59	♂	106	56	+	Rheumatic heart disease
M. S.	54	♂	111	70	+	Myocardial infarction
L. J.	68	♂	119	82	+	Myocardial infarction
J. D.	67	♂	124	89		Prostatic hypertrophy, emphysema
W. B.	62	♀	131	63		Hyperthyroidism
R. S.	68	♂	133	97	+	Metastatic carcinoma of stomach
K. S.	49	♂	134	61	+	Inferior vena caval obstruction
B. H.	67	♂	178	70	+	Cerebral thrombosis
M. J.	50	♂	182	124	+	Pulmonary fibrosis and insufficiency
F. S.	55	♂	191	61	+	Hypertension
G. B.	58	♂	206	78	+	Hypertension
E. S.	48	♂	210	88	+	Angina pectoris
T. B.	74	♀	231	126	+	Metastatic carcinoma of breast
G. H.	45	♂	242	73	+	Angina pectoris
E. M.	60	♀	550	162		Nephrotic syndrome
L. T.	44	♂	>500	102		Amyloidosis, nephrotic syndrome
J. B.	65	♀		84	+	Cerebral thrombosis, hypertension
M. C.	53	♀		76		Vascular tumor of brain
J. H.	54	♂		70	+	Hypertension, aneurysm of Circle of Willis
A. H.	63	♀		62		Chronic cystitis
V. V.	74	♂		76	+	Diabetes, Parkinsonism
O. W.	70	♂		78	+	Carcinoma of prostate
Mean	60			81		

From data of Perry, Schwartz, Hager and Schroeder.

NOTE: The iodine number of human depot fat is 64 (348) and cholesterol is 65.8. The mean iodine number of fatty acids in plasma of normal Chinese is 156.6 (8).

TABLE XLIV

COMPARISON OF DESIGNATIONS OF LIPOPROTEINS SEPARATED BY VARIOUS TECHNICS*

Ultracentrifuge		*Electrophoresis*	*Cohn Method Fraction-10*	*Barr, Russ & Eder*
Solvent Density				
1.063 (Gofman, *et al.*)	1.21 (Lewis, Green & Page)			
Symbol				
S_f	$-S_{1.21}$			
20–100+	>70			
10–20	40–70			
3–8	25–40	Beta Globulin	I, III	C
1–3	20–25	Alpha—2		
	2–8	Alpha—1	IV, V, VI	A

Note that the use of a solvent density of 1 063 does not permit alpha-1 lipoprotein to undergo flotation It is not certain which Cohn fraction contains the lipoprotein identified ultracentrifugally as alpha-2.

* From Furman (352).

best, these molecules are "secondary invaders" or carriers and probably are not as directly concerned with pathogenesis as is cholesterol and its synthesis. If the total amount of cholesterol to be carried were low, there would be little or none to be deposited. The nature of the fatty acids in phospholipids also may be more important in atherogenesis than the total quantity. We must go deeper into first causes than a consideration of carrier components

in the blood. What they are and what they are made of is of the greatest importance.

The lipoproteins carry steroid hormones, cholesterol and its esters, carotene or vitamin A, α-tocopherol, and acetal lipid (containing hydroxyl groups) (352, 353, 387). Most (75 per cent) of the "free" cholesterol in serum is in the β-lipoprotein fraction as is the esterified fraction (73 per cent), while less (55 per cent) of the phosphorus is in this fraction. Barr found somewhat lower values in β-lipoproteins (354, 355). Thus, increase in the cholesterol-phospholipid ratio, suspected to be of atherogenic significance, means, in terms of lipoproteins, that with relatively less phospholipid than cholesterol, the β-lipoprotein fraction will be increased in the proportion of 1:1.35. Gofman finds that particles of the S_f 10-20 classes have weight ratios of cholesterol to phospholipid as high as 1:1.3 (356).

Exogenous Cholesterol: There is *no evidence* that a *diet containing* reasonable amounts of cholesterol (up to 1 0 Gm per day or the equivalent of four eggs) influences the level of blood cholesterol (357). Feeding healthy volunteers (358) or patients (359) up to ten times that amount causes insignificant changes in plasma levels.* Actually, at 200 mg. per 100 ml. blood, there is about 8 Gm. *in* circulation with an additional 3 to 4 Gm. *in* liver and a considerable amount in other tissues While exogenous cholesterol probably little affects plasma levels in man, the reverse, i.e., restricting the dietary intake to very low values, does decrease plasma levels, since all dietary cholesterol is contained in fatty foods which therefore need

* It is possible to block some of the intestinal absorption of exogenous cholesterol by plant sterols, such as sitosterol in large doses The effect on plasma cholesterol, however, is either insignificant, or significant to a very minor degree.

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Symbol				
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usually contain unsaturated fatty acids. This is not true of fish oils, which must be largely unsaturated or short chain because of the low melting point essential for mobility of the animal at low temperatures. Actually fish fat contains several very long chain unsaturated fatty acids.

There are three habits largely common to the U.S.A. and some European countries which tend to raise the dietary intake of saturated fats (202, 348, 360). 1) Since 1920, animals fattened for slaughter have been fed high carbohydrate diets in order to lay down a hard fat. Meat from animals eating unsaturated vegetable fats is oily and housewives do not like to buy it; the melting point is low. 2) For many years, vegetable fats (unsaturated) have been commercially hardened, often by a copper or nickel catalyst, in order to provide shortenings or margarine which are solid at room temperatures. 3) The consumption of milk, butter and cheese has increased; milk fats contain shorter chain saturated fatty acids and are believed to be atherogenic (356)

Relation of Dietary Fats to Cholesterol: Why does an excessive intake of hard or saturated fats cause atherosclerosis? The following information is known.

1 Animals lay down in their tissues part of the fat ingested. This has been demonstrated in all mammals but man. Pigs fed very long chain, high melting point fatty acids may crack in the cold. Unnatural fats (odd numbered carbon atoms or optical isomers of natural fats) can be recovered from the bodies of animals to which they are fed in amounts from 10 to 25 per cent (348).

2 Cholesterol esters can be formed of the type of fat in the diet. Thus, stearic or even unnatural fatty acid esters of cholesterol can be recovered when a specific fat is fed (348).

3 The esters of cholesterol in blood usually contain

be severely restricted. In animals, however, especially rats, rabbits, monkeys and chickens, very high intakes (2 to 4 per cent of the diet) raise plasma levels markedly (356).

Type of Fat Ingested: The weight of evidence at present is in favor of the idea that a diet high in fats of animal origin is atherogenic, while diets containing adequate but relatively smaller amounts of vegetable fat are not. Although there are many types of fat in both animal and vegetable sources, the number is somewhat limited by the digestibility of the fats with higher melting points. Natural fats contain an even number of carbon atoms and are usually found as triglycerides; the lengths of the chains vary from 4 to 24. Some are saturated, some contain one, two, three or four unsaturated ethylene linkages. Obviously an enormous number of possible combinations can occur; fortunately, in nature they do not (Table XLIV).

The melting points of the saturated fatty acids are directly proportional to the length of the carbon chain, short chain acids being liquid (348). Equal length unsaturated acids have lower melting points. Solubilities are directly related, the saturated acids being less soluble in water and alcohol. Furthermore, the specific gravities of saturated fatty acids are lower than their unsaturated relatives.

Insofar as is known, there is no difference between glyceryl tristearate obtained from animal sources and that derived from vegetable; the fatty acids are identical. Fully hydrogenated linolenic acid becomes stearic acid. What then are the differences? Unless vegetable oils contain some esoteric product which counteracts the atherogenic influence of animal fats, we must look to the composition of the fats themselves. In general, animal fats have more saturated fatty acids than vegetable fats, while the latter

usually contain unsaturated fatty acids. This is not true of fish oils, which must be largely unsaturated or short chain because of the low melting point essential for mobility of the animal at low temperatures. Actually fish fat contains several very long chain unsaturated fatty acids.

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2. Cholesterol esters can be formed of the type of fat in the diet. Thus, stearic or even unnatural fatty acid esters of cholesterol can be recovered when a specific fat is fed (348).

3. The esters of cholesterol in blood usually contain

more unsaturated fatty acids than do neutral fats or phospholipids (360).

4. The metabolism of cholesterol and that of the essential fatty acids is closely interrelated. Essential fatty acid deficiency in rats is accompanied by storage of cholesterol in liver and adrenal. Diets low in fats may lower blood cholesterol but increase that in liver. Linoleate or linolenate either may be required to mobilize depots of cholesterol, or be necessary for its catabolism (360, 361).

5. Blood and liver levels of cholesterol in rats are elevated in essential fatty acid deficiency when cholesterol is fed. Methyl linoleate lowers both values (360).

Cholesterol is synthesized in the liver, adrenal and presumably other tissues from acetate. The possible pathways are shown in Figure 19. Obviously it is impossible to avoid acetate, which is a metabolic product of fat, carbohydrate and amino acid metabolism. The immediate precursor of

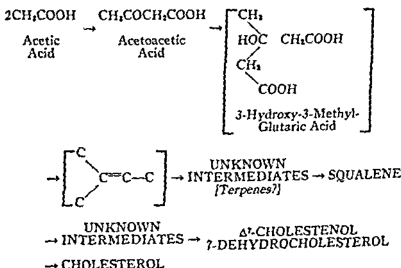


Fig. 19. Possible pathway of cholesterol synthesis. Entirely hypothetical intermediates are enclosed in brackets. (From Langdon: In *Fat Metabolism*, V. A. Najjar, ed., Baltimore, Johns Hopkins Press, 1954.)

TABLE XLV

COMPOSITIONS OF CORN, COTTONSEED, OLIVE OILS AND BUTTER*

	Corn	*Cottonseed*	*Olive*	*Butter*
Iodine number	103–129	90–110	79–90	26–38
Saturated acids (%)	12–18	21–32	9–19	30–43
Oleate	21–49	19–36	64–86	28–41
Linoleate	34–61	34–56	4–15	
Linolenate	0–2 9	0	0	0
Arachidonate	0	0	0	0
Squalene (mg %)	28	8	383	0
Ergosterol	+	+	0	+
Sitosterol	+	+	0	
Stigmasterol	+			
Rate of enzymic hydrolysis	1	2	3	
Tocopherol (mg %)	87–250	83–110	3–30	

* After Deuel (348) and Eckey (447) Contents vary with climate, soil and seed

cholesterol has been shown to be squalene, a hydrocarbon with six double bonds having the empirical formula $C_{30}H_{50}$ (362) Squalene is found in the unsaponifiable fraction of several, but not all fish oils and only one plant oil, olive oil (0.41-0.54 per cent). Other vegetable oils contain only very small amounts (peanut oil 0.07 per cent). Animals fed labelled squalene synthesize cholesterol 50 times as efficiently as when given labelled acetate (362). Squalene is not converted to fatty acids, as is acetate. Another precursor of cholesterol is provitamin D_3, or 7-dehydrocholesterol, widespread in foods but in small quantities.

Effect of Various Fats on Blood Cholesterol Levels in Man: One can gain some information on the relationship of the type of fat ingested to the level of cholesterol in plasma by human experiments, in which dietary fat was markedly increased (Table XLVI). If these results are valid, an examination of the table points at once to specific dietary factors or the lack of them which alter cholesterol

TABLE XLVI

DIETARY FACTORS ALTERING PLASMA CHOLESTEROL IN MAN*

Factors Causing Increased Levels	*Factors Causing Decreased Levels*
High fat intake	Low fat intake (386)
Starvation	Scurvy
Low carbohydrate intake	Vegetable fat (Diabetics)
Vitamin B deficiency	Soy bean oil (446)
Vitamin B_6 deficiency (monkey)	Sunflower seed oil (448)
Olive oil	Nuts (363, 365)
Cottonseed oil	Corn oil (367, 368)
Butter (368)	Brain extract (366)
No change caused by: Obesity; Cholesterol intake (357) (moderate)	

* After Deuel (360) and others.

levels in man. Vitamin B deficiency, starvation, low carbohydrate intake, "high fat" intake, olive and cottonseed oils and butter move cholesterol values in the same direction, up, while specific factors appear among those reducing it. Because corn and olive oils act oppositely, we must look to differences in content of specific factors in these two fats.

The outstanding difference appears in the linolenic content, which is absent in olive and cottonseed oils* and is present to the amount of 0.6 per cent of corn oil. This essential fatty acid is not found in butter unless it is fed to the cow; it was present in one sample of American human fat and serum (348) (possibly influenced by diet) but was not found in one German (348), is in some lecithins, and cannot be synthesized by the animal (Table

* Oils may vary in their atherogenic properties, possibly because of variations in essential fatty acid (linolenate?) content (445). Olive oil consumed in Spain is usually adulterated with soy oil.

XLVII) Arachidonic acid, a normal component of animal tissues, lecithins, cephalin, phosphatides and fats, is another essential fatty acid formed from linoleic, probably by a vitamin B_6 enzyme system (349).

Therefore, the factor in certain vegetable fats (and not others) which lowers blood cholesterol may not lie in the presence or absence of unsaturated fatty acids themselves,

TABLE XLVII

ESSENTIAL FATTY ACID CONTENT OF SOME EDIBLE OILS (%)*

Food	*Linoleic*	*Linolenic*	*Production*†
Linseed	15–43	40–53	2 2
Peanut	47–72	0	3 9
Sunflower	44–75	0.1	2 0
Sesame	40–48	0	1.5
Soy bean	52 0	2.3–11	3 8
Coconut	1–2	0	4 6
Animal fats	+	0	17 8
Rapeseed	12–16	7–10	3.3
Palm	6–11	0	3.3

* After Eckey (447) †Estimated World, 1951, billions of lbs.

but in the linolenic or other specific fatty acid content. The cholesterol-lowering diets of Kinsell *et al.* contain nuts in large amounts (363) The fat from some nuts, especially walnuts, contains linoleic and linolenic acids (348). In this respect, Kinsell's diets (364, 365) contained soybeans, soy lecithins, soy sauce, corn oil and walnuts, all containing linolenic acid, while this fatty acid has not been found in peanuts, almonds and cashew nuts (348). The hydrogenated oils in margarine, Crisco and peanut butter, as well as cottonseed, peanut and olive oil, which apparently do not contain linolenate were also given; in spite of these fats, at least two of which usually raise blood cholesterol, it fell. Brain extract, probably cephalin, which

contains arachidonic acid, also has been reported to lower cholesterol (366). The common denominator of the effects of these various conflicting data appears to be in the tri- or tetraethenoid acids similar to linolenic and arachidonic (367-369) (Table XLVIII).

TABLE XLVIII

FOODS CONTAINING LINOLEIC, LINOLENIC AND ARACHIDONIC ACIDS*

	Linoleic (C_{18}, 2 double bonds)	*Linolenic (C_{18}, 3 double bonds)*	*Arachidonic (C_{20}, 4 double bonds)*
Egg yolk lecithin	+	0†	+
Brain lecithin	0	0	+
Brain cephalin		0	+
Liver lecithin	0	0	+
Pig fat	+	0	2.1%
Butter fat	3.6–4 5%	?**	+
Fowl fat	21.3%	0	+
Fish	40±%	+	+
Soy bean lecithin	+	+	0
Phosphatidic acids	+	+	0
Walnut oil	73%	3–8%	0
Beechnut oil	38%	0.4–2.9%	0
Soy bean	52 0%	2 3%	0
Alfalfa	67 5%	20 8%	0

* After Deuel (348).
† Only when fed to hens.
** Only when fed to cows.

It is interesting that atherosclerosis is unusual in countries where soy beans are a staple article of diet. If these deductions are correct, substances containing linolenic acid, either in fats or in phosphatides, should lower blood cholesterol.* The relationship between pyridoxal and the formation of linolenate will be discussed below.

* The practice of fasting by some religious groups during one day a week and the Lenten season may have logic in terms of essential fatty acid

Pyridoxal and Trace Metals: The amount of vitamin B_6 in the diet has a definite influence on essential fatty acid metabolism in animals Vitamin B_6 deficiency and essential fatty acid deficiency in rats resemble each other grossly, and each factor will partly alleviate the other. There are, however, fundamental differences in enzymes in the two

TABLE XLIX

COMPARISON OF ESSENTIAL FATTY ACID AND PYRIDOXINE DEFICIENCIES IN RATS (384)

Function	*Organ*	*Essential Fatty Acid*	*Pyridoxine*
Respiration	Liver	Increased	
Cytochrome oxidase	Liver	Increased	Increased ±
Succinic oxidase	Liver	No Change	No Change
Phosphate esterification	Liver	Decreased	Decreased
Glutamic dehydrogenase	Liver	Decreased	Decreased
Butyric dehydrogenase	Liver	Decreased	No Change
Succinic dehydrogenase	Liver	Decreased	No Change
Glutamic decarboxylase	Brain	—	Decreased
Arachidonic synthesis	Carcass	Decreased	Decreased
Hexaenoic synthesis	Carcass	Decreased	Decreased
Octanoate oxidation	Carcass	—	Decreased

conditions (Table XLIX). Apparently, vitamin B_6 is essential for desaturating partly unsaturated fatty acids, such as linoleic, further to synthesize arachidonic, and in metabolizing linolenic to hexaenoic acids. Linoleic is a precursor of arachidonic and linolenic of the hexaenoic acids (349).

deficiency or saturated fatty acid excess Thus, the members of the Russian Orthodox Church eat nothing of animal origin during Lent, Advent and on Wednesdays and Fridays and *use oils high* in linolenic acid. Roman Catholics, by custom, supply themselves with adequate essential fatty acids on Fridays and during *Lent*, but do not restrict other animal fats. Mohammedans have strict dietary laws *during Ramadan*. In terms of deposition of lipid these religious habits probably do no harm in maintaining or restoring the integrity of the intima.

In deficiency of this coenzyme, liver fat becomes more saturated (370).

Snell believes that vitamin B_6 as a coenzyme contains a metal for activity (215). If so, the interrelationships are obvious, although whether or not such a metalloenzyme acts in the fatty acid cycle is not known. The only one of these enzymes containing a metal is acyl-Co-enzyme A dehydrogenase, which uses copper.

Some further information may be obtained by the use of metal binding and chelating agents in lowering blood cholesterol. Calcium disodium ethylenediamine tetraacetate (EDTA) is a good cholesterolytic agent in man (Figs. 20-21), sometimes lowering values to the Indian "normal" (180, 371, 372). In rabbits (373) and rats (374) fed cholesterol, however, it raises blood levels above the controls, and in rabbits but not in rats, it prevents deposition of this lipid in the liver. Because EDTA is not metabolized in the body and diffuses readily (250), its sparing effect on liver but not on blood levels must be related to removal of one or more trace metals. EDTA also raises lipid synthesis by rat liver while another agent, 8-hydroxquinoline, lessens it (375). EDTA causes marked loss of subcutaneous and depot fat (376), suggesting that a metal is involved in fat metabolism and synthesis. Hydralazine, another metal binding agent, also lowers cholesterol in man (180) (Fig. 22).

Comment: These indirect but quite suggestive data are provocative of thought when viewed in pathogenetic and therapeutic terms. Obviously, normal cholesterol levels are lower in some countries than in others, usually in those less touched by Western Civilization. If we could reduce our own to these "normal" values by interfering with the processes which raise them to abnormal levels,

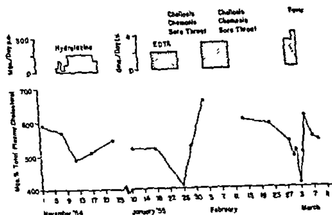
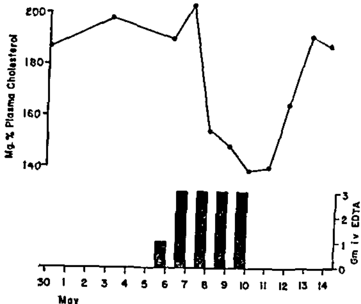
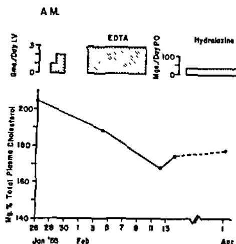


Fig. 20 Effects of oral hydralazine and intravenous EDTA on plasma cholesterol levels L. T, 44 years of age, was seen in October, 1954, because of mild exertional dyspnea and ankle edema for six months. At 7 years of age he had Marie-Strümpell arthritis, and at 25 years of age, migratory polyarthritis without urinary symptoms. Nephrosis was clinically evident, and amyloidosis was proved by renal punch biopsy To lower his plasma cholesterol, hydralazine was begun without evident clinical improvement. In a further effort to lower his plasma cholesterol, three courses of parenteral EDTA were given. On the sixth day of this first course of therapy, slight inflammation of the mucous membranes and a magenta tongue were observed, and he complained of soreness about his mouth and gums. By the final day, cheilosis, chemosis, scrotal inflammation, and pustular lesions over the face and trunk had appeared Within a week, the lesions had vanished and a second course of EDTA was begun On the fourth day, stomatitis reappeared and within 7 days the same syndrome was present again necessitating the discontinuation of therapy. The 3-day final course produced no such lesions, however, fever immediately followed the dosage increase to 4 Gm. Cholesterol values for the second course were not plotted because such a low plasma level was attained that a laboratory error was suspected (303 mg per 100 ml. on a single determination). The changes in cholesterol preceded clinical toxicity (From Perry, H. M., Jr., and Schroeder, H. A.: *J. Chronic Dis.*, 2:520, 1955) Metal excretion in Table XXX, p. 160.





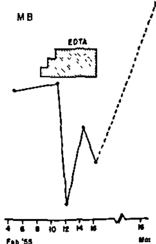


Fig 21. Effect of intravenous EDTA on plasma cholesterol. The material was given as the calcium disodium chelate. L S, The patient's diabetes, controlled on 45 units of insulin a day, worsened to the point that it needed 55 units, possibly a result of pancreatic loss of zinc. (From Perry, H. M., Jr, and Schroeder, H. A.: *J. Chronic Dis.*, 2:520, 1955.) A. M., Hydralazine, given in small doses appeared to maintain the lower values achieved with EDTA. M B., The rebound in a month is obvious.

we would expect little or no atherosclerosis, especially of our coronary arteries.

There appears to be something in certain but not all vegetable fats which lowers blood cholesterol markedly in man, while animal fats, hydrogenated vegetable fats and other vegetable fats with a lower iodine number raise plasma cholesterol. As a first guess, this substance may be linolenate, an essential fatty acid. If that is so, Europeans and Americans may be suffering from a relative essential

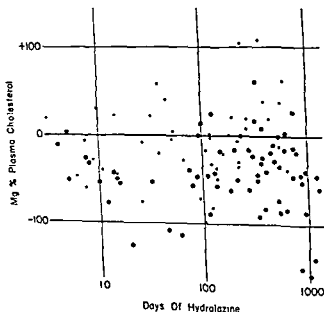
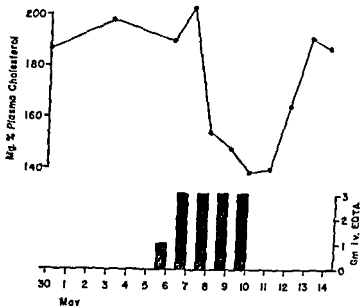
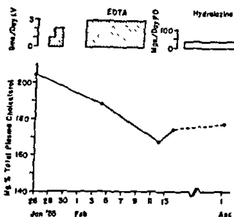


FIG 22 Effect of oral hydralazine on total fasting plasma cholesterol in 112 hypertensive patients. Changes in cholesterol concentrations before and after hydralazine are plotted against the length of therapy. Each large dot indicates a patient with an initial cholesterol level of more than 215 mg per 100 ml. plasma. Each small circle indicates a patient with lower initial values below 211 mg. per 100 ml. plasma. (From Perry, H. M, Jr., and Schroeder, H. A.: *J. Chronic Dis.*, 2.520, 1955)





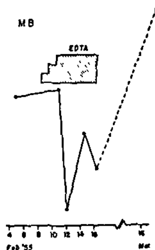


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...e	×	Intimal Injury due to a) Vitamin B_6 deficiency b) Excessive hypertension c) Normal pressure differentials	×	Increased Saturated over Unsaturated Fatty acid esters of cholesterol, lipoproteins and phospholipids. Increased synthesis or decreased destruction of cholesterol due to metals or fatty acid deficiency	×	Blood Pressure	= Atherosclerosis

The nature of the vitamin B_6 deficiency and its possible relation to trace metals has already been discussed. The plasma lipids under consideration include: a) Cholesterol esters, which are said to be usually of unsaturated fatty acids, although esters of equal length saturated fatty acids are lighter and more insoluble. Dietary excess of the latter could influence their nature. b) Lipoproteins, or protein-fatty acid complexes, the nature of which are unknown. The saturated fatty acid esters should be lighter and more insoluble than their unsaturated counterparts. If so, they should centrifuge more slowly (or float more rapidly). A lipoprotein with a specific flotation rate of S_f 0-10, if its fatty acid became saturated, should theoretically change to the S_f 10-20 class, unless rearrangement of the molecule took place. c) Phospholipids, the fatty acid components of which depend partly, perhaps, on dietary intake, but usually are formed of unsaturated fatty acids in functioning tissue (brain and liver).

Effect of Sex: For some unknown reason [illegible] women are quite immun[illegible] The disorder, however, [illegible] after the menopause as in men. Coronary occlusion in a normotensive, menstruating woman was formerly extremely rare, although cases are now appearing. The degree of aortic atherosclerosis, however, shows little sex

fatty acid deficiency. There may be very little linolenic acid in the American diet. Pyridoxal is concerned with *the utilization of essential fatty acids, and a deficiency of* one may enhance a deficiency of the other. Furthermore, trace metals can be involved, since they affect fat synthesis and may be concerned in vitamin B_6 enzymes, although their role is possibly of only secondary importance.

The differential effects of metal chelating agents must be explained. Let us assume that in the livers of human beings there is a metal (chromium, for example) which stimulates the formation of cholesterol and fatty acids, or a metal (copper, for example) which depresses catabolism of lipids, in addition to the normal metal (manganese, for example). EDTA, because of its higher affinity for the abnormal metal, removes it, allowing synthesis to revert from an accelerated to a normal rate or catabolism to raise itself to normal. In the animal fed cholesterol, however, there is no abnormal metal affecting synthesis, therefore the normal one is removed. In that event, the synthesis of cholesterol in liver might be lowered or catabolism raised, preventing accumulation of endogenous cholesterol in liver but allowing exogenous cholesterol to remain in the blood. The latter would be the case if storage and synthesis were related. The differential effects of EDTA and 8-hydroxyquinoline in the rat can be explained by different affinities of the two substances for metals, the former being the stronger chelating agent. That two antagonistic metals may influence an enzyme system is well known for actomyosin (Mg and Ca) and has been proposed by the Bernheims for lipid metabolism (Mn and V) (274).

These various factors can be substituted in Friedman's schema to include a more definitive but much more hypothetical one.

fluctations can occur (377). A persistently high level is atherogenic; a momentary low level may not reflect the true state of affairs in terms of intimal exposure. There are conflicting opinions and data, but the opposing views can be resolved by realization that: a) cholesterol levels fluctuate and unless consistently elevated, values may be meaningless; 2) when a patient is sick, the levels fall; 3) the full lesions of atherosclerosis develop only after prolonged, constant or intermittent hypercholesterolemia.

In this chapter we have spoken of trace metal imbalances, conditioned vitamin B_6 deficiencies, and essential fatty acid deficiencies. We have emphasized that these deficiencies are relative, conditioned and local to one or at most a few enzyme systems. There is no practical way, however, of reversing vitamin B_6 deficiencies at the present time. The administration of 50 mg. of pyridoxal hydrochloride daily to many patients has not resulted in a detectable fall in blood cholesterol. The administration of at least two trace metals, cobalt and manganese, in large daily doses have not caused clinical changes detectable by ordinary laboratory methods. Only by chelating agents have we been able to affect blood levels favorably (180).

The several pathogenetic factors outlined by Friedman *et al.* should be affected simultaneously if we are to expect cessation of the process or, at the best, reversal. Whatever is making the intima injured so that plaques are formed should be opposed; as an approximation, pyridoxine in adequate doses is required until more is known. The abnormally high cholesterol levels in blood should be reduced by dietary influences and chelating agents, if possible. Elevated diastolic pressure should be controlled at normotensive levels. Under these conditions, some reabsorption of plaques which are not too scarred might be expected.

difference (355). These differences cannot be explained by gross differences in plasma lipids, cholesterol or phospholipids, but lower concentrations of beta-lipoproteins, higher ones of alpha-lipoproteins and lower "atherogenic" ultracentrifugal lipoproteins are found in women. The administration of estrogens to men alters these values to those of healthy young women, while methyl testosterone acts in the opposite direction. Estrogen shifts an appreciable amount of cholesterol carried by beta-lipoproteins into alpha-lipoproteins while testosterone does the opposite. The same sex immunity to coronary disease is found in chickens. Although estrogen is carried in blood by lipopoteins, this phenomenon is unexplained on a mass action basis by the small amounts administered.

Clearing Factor: Heparin will "clear" lipemic serum both *in vivo* and *in vitro* (444). Apparently this anticoagulant alters the physicochemical structure of chylomicra so that they become soluble. These large fat-filled particles carry almost all dietary cholesterol. The rates of clearing are faster in young women than in men and slower in the aged. Their relations to atherosclerosis are not known.

CLINICAL IMPLICATIONS

At present there are several available methods for lowering blood cholesterol in man. Because the pathogenesis of atherosclerosis is a multi-valent one, the process must be attacked at different levels. Obtaining a permanently lowered cholesterol level in blood might allow cessation of the deposition of cholesterol in plaques with probably some absorption in the presence of an altered gradient between plaque and plasma. Practical methods will be discussed in Chapter IX.

What the level is at any one instant of a lifetime of exposure to atherosclerosis is relatively unimportant. Wide

3. Ischemia due to organic vascular disease, which does not appear until the pressure is lowered, is a clear and present hazard; in actual practice it is rare.

4. Diastolic normotension must be achieved and maintained whenever possible. A compromise is hazardous, merely modifies the disease, promotes drug tolerance and does not allow eventual reduction of dosage.

5. The use of any ganglionic blocking agent, the action of which does not last for 24 hours, requires that blood pressure be measured before each dose in order to prevent a) hypertension, b) hypotension, and c) to provide as constant a blood level as possible throughout the day and night. Varying requirements and absorption necessitate varying dosages according to the prevailing levels of blood pressure.

6. Arterial hypertension due to increased generalized vasospasm is a disorder or a disease. The patient either has it or has not. If he has, severity varies widely from slight to marked. Therapy should be applied when both patient and physician want to control the disease. If therapy is not applied, the responsibility rests on the physician that the disease is not doing or going to do harm.

EVALUATION OF PATIENT FOR DRUG THERAPY

The first question to be answered is: Has the patient hypertension? A diastolic pressure of 90 mm. Hg or over (measured by the disappearance of Korotkoff sounds) is strongly suggestive, in fact usually indicative, of generalized vasospasm in the absence of tachycardia, polycythemia or coarctation of the aorta. When persistent, it suggests chronic hypertension; when relieved by relaxation, it suggests the "prehypertensive state."

The second question is: How severe or sustained is the

Chapter VIII

PRACTICAL METHODS FOR MODERN THERAPY OF HYPERTENSION

INTRODUCTION

On the basis of the various hypotheses and findings outlined in previous chapters, and using the potent drugs discussed, a practical method of controlling excessive vasospasm in man can be outlined and the therapeutic limits of a long-term regimen can be predicted. While the use of this regimen requires care and precautionary measures, it is no more difficult, in fact much less so, than is the control of diabetes mellitus. Some simple but basic rules need be kept in mind, which any practitioner of medicine can follow. The results are often life-saving in severe cases.

General Rules: 1. Vasospasm alone is being treated. In no case are the results of atherosclerosis (coronary and cerebral arterial narrowing, the loss of aortic elasticity, renal arteriosclerosis) being reversed, as far as we know, although there may be slow changes with time. Therefore, the most striking results will be seen in cases where the effects of vasospasm are the greatest (hypertensive heart failure, cerebral edema), and the poorest in cases where the effects of atherosclerosis are the most advanced.

2. In all cases where two different factors are contributing to the generalized vasospasm, two differently acting drugs must be used. When only one factor is operating, only one drug is necessary. In severe hypertension two factors almost always are functioning.

primary organic renal diseases, adrenal dysfunction, or emotional crises.

For a thorough work-up, evaluation of the cardiac status requires a study of the symptoms, electrocardiographic tracing for left ventricular hypertrophy, strain patterns, or old myocardial infarction, and roentgen or fluoroscopic examination of the heart. In actual practice only signs of a previous coronary occlusion are important indications for cautious therapy, but physicians are often gratified to watch enlarged hearts slowly become smaller and abnormal electrocardiographic tracings revert to normal under continuous therapy.

Renal status is evaluated most easily by routine urinalysis and the intravenous injection of phenol red (PSP), with urine specimens obtained 15, 30 and 60 minutes after injection The test is simple and reliable. The bladder need not be emptied before the test, although the first specimen may show a somewhat smaller amount of PSP,* for unknown reasons. (Reabsorption of PSP by bladder wall has not been ruled out.) Adequate hydration is essential for accurate values. The urinary concentration test is impractical on an outpatient basis owing to difficulties in restricting the amount of dietary water. If the 15-minute PSP excretion is less than 10 to 15 per cent, azotemia may be suspected.

Retinoscopy is essential in all cases. The appearance of exudative or hemorrhagic retinitis is often a poor prognostic sign, making treatment mandatory. The best method for grading fundal changes is that of Keith and Wagener

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* In a series of 39 medical students paired for the test, with bladder empty the 15-minute excretion was 35.5 per cent; with bladder full, 30.9 per cent. The normal values with bladder initially empty were, 15 minutes, 35.5 per cent, 30 minutes, 21.2 per cent, 60 minutes, 17.0 per cent with a total of 73.7 per cent.

hypertension now? This can be answered only by repeated measurements of blood pressure; sometimes complete bed rest is necessary to rule out emotionally induced vasospasm. The examining physician must be aware of the "manometric reflex," a psychosomatic response by vasospasm to the wrapping of the cuff about the arm (4). He also must keep in mind the wide spontaneous variations of blood pressure sometimes seen in hypertensive individuals (388, 37, 36).

The third question is: How much harm, if any, is hypertension doing or has it done? This can be answered mainly by physical examinations and simple laboratory tests, bearing in mind the sharp division of what changes are atherosclerotic and what are the results of overwork and vasospasm. Systolic hypertension is not caused by vasospasm but by hard arteries or increased cardiac output; cerebral thrombosis and coronary occlusion are not directly hypertensive in origin.

The fourth question is: How rapidly is it progressing? An accurate history and clinical judgment supplies the answer, often only after many examinations.

Office Practice: While partial answers to these questions can be obtained in office practice, one can do better by a hospital work-up (400).

The date of onset of hypertension should be determined if possible, in order to get an idea of the rate of progression. The date of discovery may be less important. The effects of hypertension can be evaluated by inquiry into the cardiac status, dyspnea being the earliest symptom of insufficiency, and renal status, by polyuria and nocturia. The approach to the patient is divided into three parts: a) estimation of the rate of progression; b) estimate of the present status in terms of secondary organic damage, and c) inquiry into possible definite etiologic factors such as

5. External compression of the renal artery
   a. Tumors of the pedicle*
   b. Aneurysms*
6. Diminution of the calibre of the renal arteries
   a. Congenital malformations, hypoplasia*
   b. Atherosclerosis, with atheroma of the main renal artery (common)*
7. Disorders of the urinary tract
   a. Obstructive disorders
      (1) Lithiasis*
      (2) Hydronephrosis *(usually infected)**
      (3) Pyonephrosis
      (4) Congenital malformations*
      (5) Prostatic hypertrophy*
      (6) Uterine prolapse
      (7) Pelvic tumors (fibromyomata)*
   b Pyelonephritis (common)*
8. Venous obstruction
   a. External compression of renal vein
   b. Congestive heart failure*

The following intrarenal diseases must be considered:

1. Inflammatory vascular lesions
   a. Disseminated lupus erythematosus*
   b. Polyarteritis nodosa*
   c. Syphilis
   d. Thromboangiitis obliterans
2. Inflammatory renal lesions
   a. Glomerulonephritis*

The following endocrine diseases can influence hypertension:

1. Hypophyseal tumors and *hyperfunction**
2. Adrenal cortical and medullary tumors and hyperplasia*

(389); in simplest terms it means: Grade I, spasm; Grade II, spasm and sclerosis; Grade III, spasm and hemorrhage and/or exudate; Grade IV, spasm, hemorrhage and/or exudate plus papilledema. Cases between grades are naturally encountered.

The lability of the blood pressure can be tested by giving tetra-ethylammonium chloride (Etamon) intravenously, thus blocking sympathetic ganglia. This drug is not to be given in states of renal insufficiency; excreted by the kidney, it may be retained and the patient may suffer from postural hypotension for several hours.

Intravenous pyelography and repeated cultures of the urine are essential for revealing the presence of chronic pyelonephritis, if active low grade infection is present. Estimation of the numbers of bacteria per ml. of urine (colony count) is of more value than merely finding organisms.

The following renal conditions, usually discovered by pyelography or aortic arteriography, can influence hypertension unfavorably by adding a renal factor to a neurogenic one. The list was modified from that of Braun-Menendez *et al.* (148, 393, 394).

1. Reduction of renal parenchyma
   a. Polycystic kidneys*
   b. Renal tumors (rare)
   c. Hydatid cyst of kidney (rare)
   d. Traumatic lesions*
   e. Hypoplasia*
2. Perinephritis, healed*
3. Complete obstruction of main artery or branch*
   a. Thrombosis and atheromata of the renal artery*
   b. Emboli to the renal artery, clot or cholesterol*
4. Intermittent occlusion of the renal artery
   a. Renal ptosis*

* Personally observed.

EVALUATION OF GENERALIZED VASOSPASM IN HYPERTENSIVE STATES

It is of little more than academic interest what the underlying pathogenetic factors in a state of severe hypertension may be, except when chronic pyelonephritis can be treated with antibiotics (often with little success) or recurrences of glomerulonephritis prevented by antibiotics designed to abort upper respiratory tract infections. It also matters little what the type of renal disease contributing to the vasospasm may be, pyelonephritis, glomerulonephritis, secondary arteriolar nephrosclerosis or even polycystic disease. What do matter are the relative influences of neurogenic, nephrogenic or adrenocortical factors in causing the vasospasm, for the relative amounts of different drugs required will differ according to the amount of renal ischemia present. Therefore, it is a good plan to group cases according to several stages of the disease dependent upon the amount of vasospasm one finds and its lability.

The degree of lability of the vasospasm is the factor which determines these stages. Complications such as cerebral vascular accident and coronary arterial occlusion can occur in any stage, mild, severe, or normotensive, as they are caused not directly by vasospasm but by an associated disease, atherosclerosis. The fact that this other disease can be influenced by the severity of the hypertension, i.e., the vasospasm, has little to do with therapeutic measures aimed at vasospasm. Therefore, classifications based partly upon atherosclerotic damage are valid for purposes other than the choice of drugs or procedures, such as prognostic implications and for surgical risk. One would not use the most potent drugs in a patient with hemiplegia or congestive heart failure who exhibited severe atherosclerosis and mild hypertension; one would use them, however, in a patient with severe but asympto-

3. Ovarian tumors*
4. Toxemia of pregnancy*
5. Testicular tumors with hyperfunction*

The following nervous lesions can contribute to hypertension:

1. Certain tumors of brain*
2. Anxiety states*
3. Expanding inflammatory lesions*
4. Cerebral vascular lesions*

Hospital Patients: For further evaluation, the patient should be examined in hospital, both for the purpose of determining the lability of blood pressure and for initiating treatment with ganglionic blocking agents. Blood pressure is measured every 4 hours by the nurses and is charted. The sodium amytal release test is performed (0.2 Gm. sodium amytal given each hour for 3 hours, blood pressure being measured hourly during the night). The ability of the kidneys to concentrate urine also can be measured by giving the patient a dry diet and no fluids for 12, 18 or 24 hours; the last specimen shows the maximal specific gravity, corrected for proteinuria or glycosuria.

The obvious disorders causing true or false hypertension must be ruled out before starting therapy. Pheochromocytoma is a rare disease requiring a high index of suspicion; it can be suspected by using phentolamine (Regitine) intravenously without prior sedation. Regitine can cause acute hypotension and renal shut down in azotemic states. Measurement of catechol amines in urine, either by bioassay (390) or chemical determination, is a specialized procedure done only in a few medical centers. Coarctation of the aorta is unusual; palpation of the femoral arteries or abdominal aorta will usually show its presence, as will roentgenograms of the rib cage.

Serious secondary atherosclerotic complications may or may not be present; if so, about 30 to 40 per cent may be dead in 3 years. The ocular fundi are Grade I or II, renal function is normal or nearly normal, and the blood pressure is roughly 180/100 to 220/120 mm. Hg during rest in bed. Reserpine plus fairly large doses of hydralazine (300 to 400 mg. per day) will control about half of these cases eventually; the remainder require the addition of ganglionic blockade. With time, individuals in this stage uniformly exhibit reversal of the process and marked reduction of dosage; in 2 to 3 years a majority can be maintained on reserpine alone and a few will be in a complete but probably temporary remission.

Stage III is made up of individuals with Grade II to III (Keith-Wagener) ocular fundi with or without occasional hemorrhagic and exudative lesions, with severe generalized vasospasm and hypertension not relieved by heavy sedation (sodium amytal). Renal function is adequate but usually reduced. Serious atherosclerotic complications may or may not be present. The blood pressure is usually 200/120 to 270/160 mm. during rest in bed. In this stage, which usually carries a poor prognosis (40 per cent dead in 3 years), ganglionic blockade plus adequate doses of hydralazine (500 mg. or more per day) are essential for control. Reserpine may or may not be added, mainly for its sedative action in smoothing out variations in blood pressure caused apparently by emotional lability in the presence of incomplete and irregular ganglionic blockade. Therapeutic results are good, 95 per cent surviving 5 years, with considerable eventual reduction in dosages in most.

Stage IV corresponds to Perera's "accelerated phase," or what is more commonly called the "malignant stage." For therapeutic purposes it can be divided into three sub-

matic diastolic hypertension and retinitis without serious cardiovascular damage having yet occurred.

We *define normotension* as levels *below 140/90 mm.* Hg. It is at this diastolic level that vasospasm becomes slightly excessive. Definitions based on higher diastolic levels in older age groups pay lip service to the prevalence of the disease, avoiding realities. Actually, in the absence of vasospasm *the diastolic pressure falls slightly* as atherosclerosis develops, while the systolic rises.

Prehypertensive: The blood pressure is slightly above 140 mm. systolic or 90 mm. Hg diastolic at times but falls with relaxation. There are no signs of secondary damage. Chronic pyelonephritis or hydronephrosis, however, may be found in young individuals (391).

Stage I comprises patients with elevated levels of blood pressure during a physician's examination but normal or lower levels part of the time, corresponding to early stages of Perera's "uncomplicated asymptomatic phase" (392). Admission to hospital and frequent measurements by nurses combined with diagnostic procedures lower them *to normal, often dramatically (400).* Renal function is excellent and there are no findings suggestive of secondary damage. Emotional tension is present and continuous. Reserpine will effectively control about half of these cases; in the remainder small doses of hydralazine (75 to 200 mg. per day) may be necessary. We do not advocate the use of protoveratrine or available blocking agents in these individuals, for their irregularity and intermittency of action may cause hypotensive symptoms. A very long-acting ganglionic blocking agent, however, should be effective.

Stage II comprises patients with elevated levels of blood pressure at all times except under heavy sedation (sodium amytal). It corresponds partly to Perera's "symptomatic uncomplicated phase" and partly to his "complicated phase."

more theoretical benefits of dividing the dose or of using slowly absorbed increments such as are dispensed in some modern capsules than there is in dividing the dose of digitalis. It has been our practice to use 1.0 mg. per day for 1 month, reducing it then to 0.5 mg. and further reducing it to 0.25 or 0.1 mg. slowly if excessive sedation appeared. It is such a mild anti-hypertensive drug in most cases that it should not be depended upon if signs of cardiovascular damage are present. Its many side effects are listed in Chapter III, nasal congestion being the most prominent and paranoid depression with suicidal tendencies the most dangerous. This latter "side effect" places it among the agents indirectly hazardous to life; the self-satisfaction of a physician using it in severe and malignant stages, who is afraid to employ more potent measures, also makes it less directly hazardous. At the first sign of increasing nervousness, anxiety, insomnia, emotional tension and agitation it should be discontinued, for agitated paranoid depression may develop (70-72). *In our experience*, reserpine is not a very valuable agent for hypertension except as a curious kind of sedative with many side effects (Fig. 24).

Reduction in dosage will often alleviate the usual depressive effects of the agent and may reduce the number of nightmares, but nasal stuffiness can be most annoying. Epistaxis induced by the drug usually necessitates discontinuation. The time-tested sedatives are the only alternatives to replace reserpine, if it cannot be used.

We have seen four patients whose severe hypertension was "cured" for several months in that all drugs but reserpine were slowly discontinued during 2 to 3 years. In one an ulcer developed; in two, inactive ulcers became active, one having a massive hemorrhage and perforation into the pancreas requiring partial gastrectomy; in the fourth

stages: (a) early, in which hemorrhagic and exudative retinitis is present but not marked (Grade III to IV) and renal function is reduced but adequate; (b) severe, in which retinitis is advanced (Grade IV) and renal function is borderline, and (c) azotemic, in which nitrogen retention has occurred. The diastolic pressure is usually 130 mm. or more and "fixed" and albuminuria is usually present. Each sub-stage carries a different prognosis, 3-year survivals of treated patients being roughly 100 per cent for (a), 80 per cent for (b) and 50 per cent for (c) without frank uremia. Ganglionic blockade plus adequate doses of hydralazine (500 to 1000 mg. per day) are essential for reversal of the stage. In general, control of hypertension is easier to achieve and is more even than with patients in Stage III; reduction of dosage is the rule after 12 to 18 months except in azotemic individuals. The systolic pressure can usually be maintained at or near former diastolic levels.

SPECIFIC USE OF DRUGS

Use of Reserpine: Reserpine is given in one dose a day, usually at night (Fig. 23). Since the effect of this drug is cumulative (although the drug itself is not), there are no

YOHIMBINE RESERPINE

Fig. 23. Chemical structures of Yohimbine and Reserpine according to Schlittler *et al.* (442).

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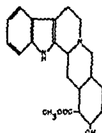
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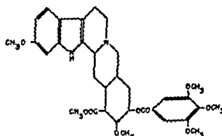


FIG. 23. Chemical structures of Yohimbine and Reserpine according to Schlittler *et al.* (442).

serious mucous colitis and proctitis with ulceration and bleeding appeared and remained. Because reserpine produces relative parasympathetic overactivity, it may be contraindicated in such individuals,* and complications such as these must be watched for.

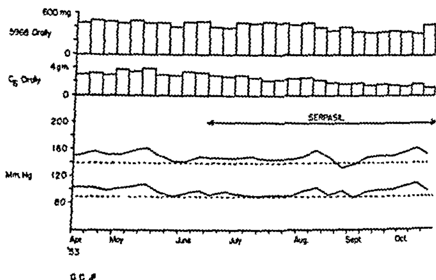
Use of Protoveratrine: One can begin this agent in doses of 0.2 mg. three times a day increasing by 0.2 mg. per dose until nausea or vomiting appears (395). The dose causing nausea is then reduced by 0.1 or 0 2 mg. and the others gradually increased to the point of nausea. The emetic effect appears within an hour after the dose, often sooner. Wide swings of blood pressure occur, with a rise at night. This agent cannot be given effectively every 4 hours, as tolerance soon develops, only to disappear with a few hours rest. To be completely effective,

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* These developments stimulate speculation If psychosomatic influences are blocked in one somatic nervous pathway, the sympathetic, perhaps [illegible] gets another Reserpine may thus be an accessory etiologic agent.

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been on [illegible] le[illegible] H[illegible] or [illegible] ch[illegible] reserpine was added, the average level of blood pressure appeared to rise at end of the period. G C., same in a 54-year-old man with severe aortic atherosclerosis who after 1 year achieved only a fair response from initial levels of 205 to 240 systolic and 120 to 140 mm. Hg diastolic. He preferred to maintain his blood pressure at levels higher than normal and to vary his dose of hydralazine; his diastolic pressure was only slightly elevated. Note the reduction in average daily dosage of both agents without change in blood pressure when *reserpine, 1.0* mg. a day, was added. Control had been previously increased on two occasions by adequate doses. (From Schroeder, H. A.: *Am. J. Med.*, 17:540, 1954)



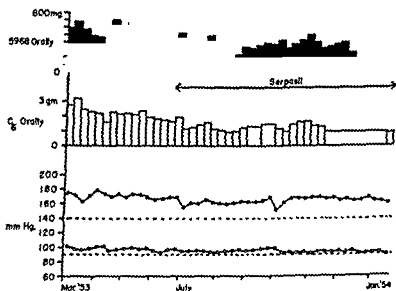


FIG. 24. Effect of added reserpine. D B., mean weekly blood pressure levels (each 35 measurements) and average daily doses of hydralazine (5968) and hexamethonium chloride (C_6) as affected by reserpine (Serpasil) 1.0 mg. per day in a patient with severe "benign" hypertension previously suffering from congestive heart failure. He had

to judge accurately the effective dose of a ganglionic blocking agent without knowing the level of blood pressure. It is most difficult to give increasing doses to maximal effect without overdosage unless the patient is under careful supervision of blood pressure and symptoms. Therefore, it is our practice to begin ganglionic blockade by drugs in the hospital, not only for convenience sake but also to achieve greatest benefit. We know of only one way to give oral ganglionic blocking agents effectively (Fig. 26).

1. Blood pressure is measured by competent nurses every 4 hours day and night, and charted.

2. Initial dose is given every 4 hours if the blood pressure is above a chosen level, usually 140 mm. systolic. It is not given if the blood pressure is below that level. Slightly higher "omit" levels are used in the cases of atherosclerotic or azotemic patients, 150 to 170 mm. Hg. Initial doses which are usually safe to give to patients with severe hypertension are: Hexamethonium chloride, 125 mg.; Pentolinium tartrate, 20 mg.; Chlorisondamine, 10 mg.; Mecamylamine, 2.5 mg.

3. If the desired normotension is not achieved, each dose is raised by increments amounting to the initial dose daily until 4 or 5 days have passed. Thus, each dose given every 4 hours will be: Hexamethonium chloride, 500 to 750 mg.; Pentolinium tartrate, 150 to 200 mg.; Chlorisondamine 50 to 75 mg; Mecamylamine, 15 to 20 mg. By this time intermittent normotension should have been achieved. (In order to change intermittency to more even control, hydralazine must be added at this point (Fig. 27).) Each "dip" in systolic pressure gives the physician confidence in the lowest levels tolerable without cardiovascular accident.

4. Doses are then given on a sliding scale, dependant on the level of blood pressure. If normotension is desired,

protoveratrine must usually be supplemented by hydralazine (Fig. 25).

Use of Ganglionic Blocking Agents: It is impossible

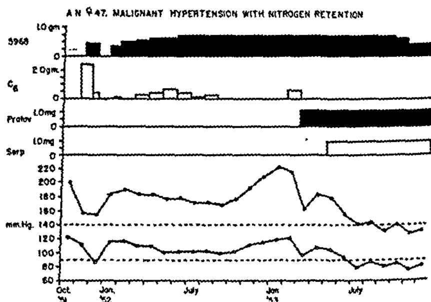


FIG. 25. Example of poor initial control of blood pressure by insufficient doses and excellent control later in a patient with malignant hypertension and renal insufficiency who also suffered from partial asymptomatic duodenal obstruction. Hypertension of 10 years' duration had become severe and grade IV ocular fundi had developed. She had suffered a minor apoplectic stroke Hexamethonium chloride induced intermittent subtotal obstruction and vomiting and was poorly tolerated after 2 months. After the initial excellent response, a grade of only a fair response was achieved on large doses of hydralazine; 1 year later blood pressure slowly returned to control levels. *The addition of protoveratrine caused a sharp decline to lower* levels; the later addition of reserpine (serpasil) produced normotension. Each point represents the average of 150 measurements. Elevated nonprotein nitrogen in her blood of 40 mg per cent (Somogyi-zinc method) had fallen to 16 mg. per cent, an abnormal electrocardiogram had become normal, and her ocular fundi had cleared. In our experience the effect of these two additional agents in severe stages is unusual. This case is illustrative of the point that control of hypertension is possible in almost all cases. (From Schroeder, H. A.: *Am. J. Med.*, 17:540, 1954.)

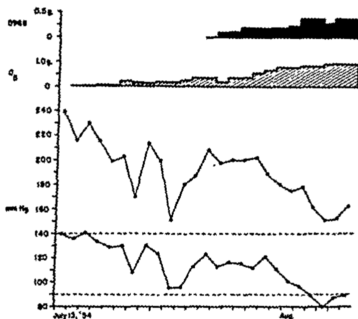
to judge accurately the effective dose of a ganglionic blocking agent without knowing the level of blood pressure. It is most difficult to give increasing doses to maximal effect without overdosage unless the patient is under careful supervision of blood pressure and symptoms. Therefore, it is our practice to begin ganglionic blockade by drugs in the hospital, not only for convenience sake but also to achieve greatest benefit. We know of only one way to give oral ganglionic blocking agents effectively (Fig. 26).

1. Blood pressure is measured by competent nurses every 4 hours day and night, and charted.

2. Initial dose is given every 4 hours if the blood pressure is above a chosen level, usually 140 mm. systolic. It is not given if the blood pressure is below that level. Slightly higher "omit" levels are used in the cases of atherosclerotic or azotemic patients, 150 to 170 mm. Hg. Initial doses which are usually safe to give to patients with severe hypertension are: Hexamethonium chloride, 125 mg.; Pentolinium tartrate, 20 mg.; Chlorisondamine, 10 mg.; Mecamylamine, 2.5 mg.

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4. Doses are then given on a sliding scale, dependant on the level of blood pressure. If normotension is desired,


H J ♂ 61 MALIGNANT HYPERTENSION.
0.5g
0
1.0g
0
240
220
200
180
mm Hg 160
140
120
100
80
July 13, '54
Aug.

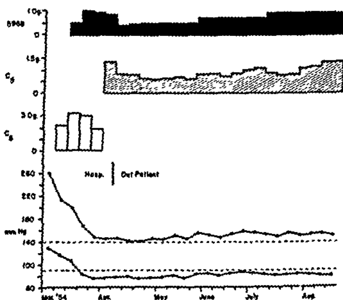

H O ♂ 60 MALIGNANT HYPERTENSION.
1.0g
0
1.5g
0
3.0g
0
Hosp.
Out Patient
260
220
180
mm Hg
140
100
60
Mar. '54
Apr.
May
June
July
Aug.

FIG. 26.



the full dose is given if the systolic pressure is over 140 mm., half the dose if between 140 and 130 mm., one-fourth the dose if 130 and 120 mm., and none if 120 or below. Higher "omit" levels 10 mm. apart are used in atherosclerotic and azotemic patients, perhaps 150, 140 and 130 or 160, 150 and 140 depending upon where the diastolic pressure has settled or whether the azotemia has lessened or worsened. Measurements are then made with the patient seated, in order to take advantage of some postural hypo-

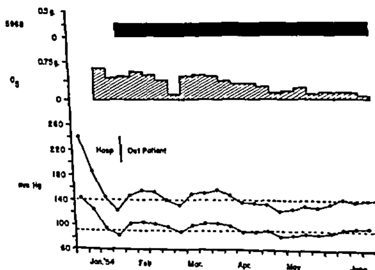
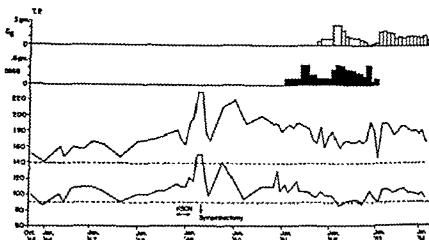


FIG 26 Examples of adequate control of blood pressure by giving adequate doses of ganglionic blocking agents (hatched area, pentolinium bitartrate, C_5) and hydralazine (solid black area, 5968). In the case of H. J., in hospital, control was poor at first until doses were raised sufficiently to achieve normotension. Each point represents the mean of six measurements. Diastolic normotension was achieved. H. O., Note increase in blocking agent required to [illegible]
tention [illegible]
hos [illegible]
dru [illegible]



E D. ♂ 48. SEVERE BENIGN HYPERTENSION.

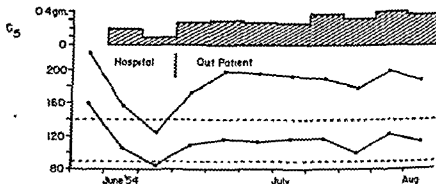


Fig. 27. Examples of failure of control of hypertension by ganglionic blockade (pentolinium, C_5) alone. E. D., Although normotension was achieved in hospital, patient died of malignant hypertension in May, 1955. Hydralazine should have been added to achieve control. T. P., Hydralazine (5968) was discontinued because of late toxicity. Although malignant hypertension was relieved and did not recur, ganglionic blockade with hexamethonium chloride (C_6) failed to maintain *diastolic* normotension. High systolic pressures were necessary because of postural hypertension resulting from drug and surgical sympathectomy. Each point is the mean of 150 measurements.

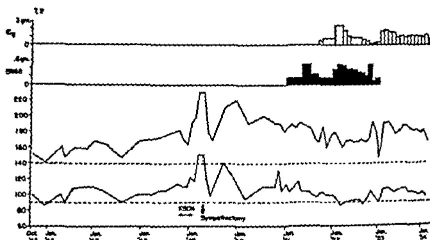
tension. Standing pressures are avoided. The night dose is omitted, leaving eight hours of uninterrupted sleep.

5. Parasympatholysis should be treated. A nightly laxative and magnesium citrate if the bowels have not moved by mid-morning will usually promote a daily evacuation. It is important to prevent distension of the intestines (404).

Precautionary measures against obstruction of a hollow viscus already partially obstructed should be taken. Abdominal scars, prostatic hypertrophy, frequent rhinitis, are warning signs of possible trouble from this source. They are usually less severe than the disease being treated. When the drugs cannot be tolerated, protoveratrine can be substituted with good results. Surgical sympathectomy, of course, does not carry this hazard. Prostatic obstruction may require surgery.

Use of Hydralazine: This drug is given almost always in conjunction with either ganglionic blockade (Fig. 28) or another milder agent acting on nerves (423). Because of initial side reactions mainly attributable to its antihistaminase action, which are lessened with nerve acting drugs, it is begun at doses of 25 mg. every 4 hours, raising the dose to 50, 75, and 100 mg. every 4 hours on 3 successive days. It is given with the blocking agent. Thus, 500 mg. a day is the usual dose in severe hypertension; we have had to give as much as 1.0 Gm. for short intervals. These large doses may cause "hydralazine disease" in 10 per cent of patients after 6 months. In general, larger doses are given for greater nephrogenic components to the vasospasm, smaller doses when the neurogenic component is large. It is unreliable when used alone (189, 396).

High fever, aching and malaise appearing during the first few weeks of administration of hydralazine requires discontinuation or marked reduction of dosage. Fortunately such sensitive individuals are rare. Angina pectoris



E D. ♂ 48 SEVERE BENIGN HYPERTENSION

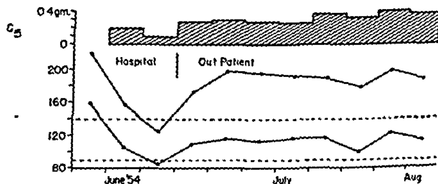


FIG. 27. Examples of failure of control of hypertension by ganglionic blockade (pentolinium, C_5) alone. E. D., Although normotension was achieved in hospital, patient died of malignant hypertension in May, 1955. Hydralazine should have been added to achieve control. T. P., Hydralazine (5968) was discontinued because of late toxicity. Although malignant hypertension was relieved and did not recur, ganglionic blockade with hexamethonium chloride (C_6) failed to maintain diastolic normotension. High systolic pressures were necessary because of postural hypertension resulting from drug and surgical sympathectomy. Each point is the mean of 150 measurements.

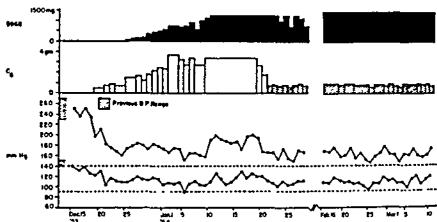
can be made worse (or relieved) by hydralazine. A compromise partial control of hypertension, by neurogenically acting drugs plus, perhaps, restriction of dietary sodium may provide some measure of vascular safety, which, while not ideal, may lengthen life. In our experience, patients with *severe* hypertension are rarely intolerant to this agent when it is first given.

Hydralazine disease appearing after 6 to 24 months of ingestion of fairly large doses necessitates two courses. Stopping the offending agent entirely results in return of hypertension; in these patients the mortality rate from hypertensive causes is 10 per cent. Large doses of ganglionic and hypothalamic blocking agents with or without protoveratrine usually fail to control the hypertension adequately; wide swings from high to low levels take place daily. This situation is about the most difficult to meet in therapy and we have no solution. Low salt diets or thiocyanate might be used; sodium azide has been valueless (Fig. 29). Closely related analogues of hydralazine have caused recurrences of the disease and chemically less related ones have been relatively worthless.

Hazards of severe restriction of dietary salt are well known. The nephrosclerotic kidney is a "salt-losing" kidney to some extent and hyponatremia with renal failure (the low salt syndrome) can be induced by limiting the intake to a point less than obligatory urinary losses. Borderline renal function predisposes to this usually fatal condition (397-399) (Fig. 30).

The second choice involves marked reduction of the dose and the possible addition of cortisone until symptoms subside. The disease resembles in part a phenomenon of depletion. By small doses blood pressure can be controlled, although "L-E" preparations may remain positive, the disease remain in a subclinical "lupoid" stage and

H.B. ♂ 46 MALIGNANT HYPERTENSION WITH AORTIC THROMBOSIS INVOLVING RENAL ARTERY



A.K. ♂ 49 SEVERE BENIGN HYPERTENSION.

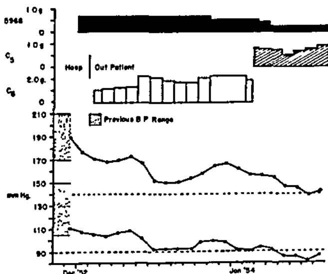


FIG. 28. Example of effect of pentapyrrolidinium bitartrate (hatched area) as compared with that of hexamethonium chloride in malignant hypertension quite resistant to the latter. Upper Curve: The patient suffered from Leriche's syndrome, proven by previous operation, which probably extended a year later to involve the right renal artery as shown by contrast aortograms. Each point is the average of six measurements made at four-hour intervals during his hospital stay (Dec. and Jan.) and of five measurements as an outpatient (a representative month, Feb. to March, is shown) Large doses of hydralazine have been required. While the result can be considered only fair, the patient worked full time on a railroad section gang without symptoms and his grade IV ocular fundi cleared. He died of uremia 2 years later. Lower Curve: Poor control of

Such is not always the case.

creased, the patient and his record are evaluated; if relative normotension is not consistent and the fluctuations of pressure much less marked, the dose of one or the other agent is adjusted upward until it is maintained. Maximal (but unusual) single doses of hydralazine can be as high as 200 mg., of hexamethonium chloride 1.0 Gm., of pentolinium bitartrate 300 mg. or more, of chlorisondamine, 100 mg. and of mecamylamine, 20 mg.

Before discharge, measurement of blood pressure with the patient seated, causes the amount of ganglionic block-

FIG. 29. Examples of hydralazine (collagen) disease with special reference to blood pressure ... hydra ... was tr ... stoppe ... had no demonstrable effect. I. W., Note strict normotension when hydralazine disease was once established. A sulfur containing ... pressure ... that of ... appeare ... but nor ... of 6, 35 ... upon the time scale.

the patient's situation be potentially precarious. Discovery of a substitute for hydralazine which will not cause this phenomenon is the only solution to the problem (Fig. 29).

Combined Therapy with Ganglionic Blockade and Hydralazine: Hydralazine is given regardless of the level of blood pressure when the two agents are used together. It disappears rapidly from the blood. At the end of the four day period during which the dose was progressively in-

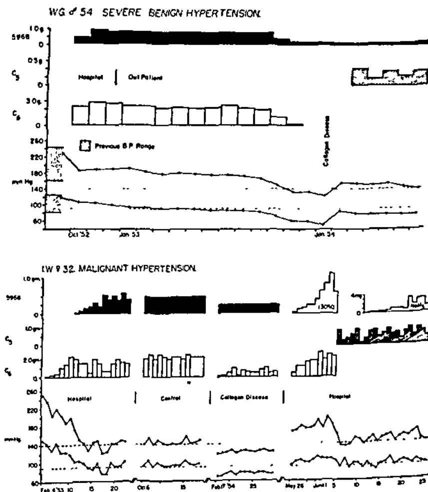


FIG. 29.

ing agent automatically to adjust itself as postural effects occur. The usual result of omission of the night dose is a rise in the morning "resting" or "basal" pressure. The patient is taught to take his own blood pressure five times a day before each dose and record it on special charts. He is instructed on the actions of the drugs and their side effects. He leaves the hospital on the same schedule, which was designed to prevent both hypertension and hypotension. By keeping a daily record, trends can be observed which are invaluable for efficient therapy. In our clinic, we examine a patient one month after discharge from hospital, and then at 3- to 6-month intervals if he is doing well. Patients seldom complain of the inconvenience, which takes about 15 minutes a day, but they do object to the cost of the drugs.

Treatment of Crises: In hypertensive crises (pulmonary edema, cerebral edema, toxemia of pregnancy), requiring parenteral administration, two lines 20 mm. apart are drawn across the graphic chart at the level at which systolic pressure is to be maintained. After initial lowering of blood pressure by a small dose of a blocking agent, blood pressure is measured every hour and a subcutaneous injection of the full effective dose given if it is above the upper line, half the dose if between the lines, and none if below the bottom line. Changes in total dosage must be made often. The second day the two lines are drawn 20 mm. lower. Thus, a patient with encephalopathy (wet brain) may have his pressure reduced from 300 mm. Hg to 220 to 200 mm. the first day, 200 to 180 mm. the second day, and 180 to 160 mm. the third day. Usually oral medication becomes possible long before this time. The pressure must be reduced more drastically when there is pulmonary edema. We prefer parenteral ganglionic blocking agents to parenteral hydralazine because of their shorter

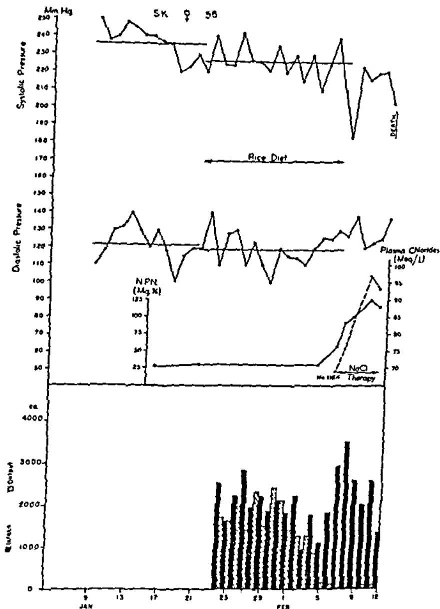


Fig. 30. A woman aged 56 had rapidly progressive hypertensive vascular disease without retention of nitrogen but with diminution of renal function. When she was given a diet containing 0.5 Gm. of salt (rice diet) obliguria developed 14 days later. This development was rapid, and the patient complained of nervousness, apathy, loss of appetite and weakness. Her intake of fluids remained high in spite of the obvious overhydration which was developing. Plasma chlorides were low, as was sodium, and an attempt to reverse the oliguria by the use of intravenous hypertonic saline solution was to no avail. She died of uremia. (From Schroeder, H. A.: *J.A.M.A., 141*:117, 1949.)

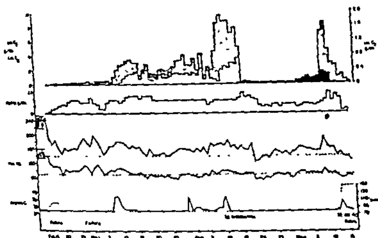


FIG. 31 Medication and vital signs during hospitalization of a 52-year-old white male with malignant hypertension and pre-treatment azotemia. The upper bar graph indicates the daily dose of autonomic blocking agent. The open bars represent oral pentolinium tartrate (po C_5). The cross hatched bars represent parenteral pentolinium tartrate (im C_5) and the solid bars represent parenteral hexamethonium chloride (im C_6). The potency of oral pentolinium tartrate approximates that of intramuscular hexamethonium chloride, however, the scale for intramuscular pentolinium tartrate has been expanded to allow for its greater effect The lower bar graph indicates oral hydralazine intake per day Daily blood pressure averages are shown, each value being the mean of at least 6, and often as many as 24, readings taken with the patient in a sitting position. The stippled area to the left indicates the pre-treatment range of blood pressure. The line graph at the bottom of the figure is a schematic representation of the vital signs The solid line shows the temperature in degrees centigrade which was below 37.5 except for three bouts of pyrexia. The dotted line shows the pulse in beats per minute which was always below 80 except for two episodes of tachycardia. The figures ind[illegible]
values [illegible]
denote- [illegible]
high d [illegible]
Perry, [illegible], Jr., O'Neal, R. M., and Thomas, W. A.: *Am. J. Med.*, in Press 1957.)

actions with less tendency to produce prolonged hypotension. In cerebral edema it may be necessary to avoid cerebral ischemia, as indicated by increasing coma, by reducing cerebrospinal fluid pressure.

Tolerance to the Action of Drugs: No tolerance seems to develop when both types of drugs are used correctly and continuously. On the other hand, tolerance is common when therapy is intermittent, an unexplained phenomenon. In the larger sense it resembles bacterial resistance to antibiotics given in less than therapeutic amounts.

One of the most difficult situations to meet is in the patient whose blood pressure has been lowered successfully, only to have the drugs discontinued because of undue alarm at side effects or the consequences of normotension (mental depression, malaise, lassitude, weakness). The hypertension which recurs immediately is much more resistant to therapy and requires much larger doses of drugs after a few days than it did initially; sometimes it seems impossible to treat (Fig. 31). We have encountered no resistance in "fresh" untreated cases; *the secret of successful therapy is continuous therapeutic pressure.* While we cannot account for this phenomenon, it is commonly observed and hazardous to the patient. Many lives have been lost by "nervous" and eratic therapy (Fig. 32).

Changes Occurring with Time: If the dose of the ganglionic blocking agent automatically falls to negligible quantities (in 6 to 18 months) by reason of sustained normotension, the dose of hydralazine is then reduced to four times a day, three times a day, twice a day and finally halved at 2- to 6-month intervals. Reduction in dosage is made very slowly (Fig. 33). The amount of reserpine is halved in a month or two if drowsiness appears, and then halved again until symptoms disappear (406).

What to Do If a Patient Is Not Doing Well: The pa-

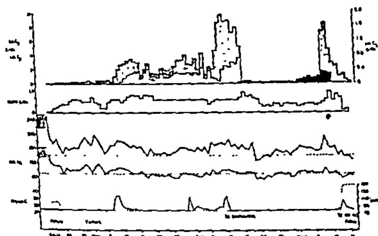


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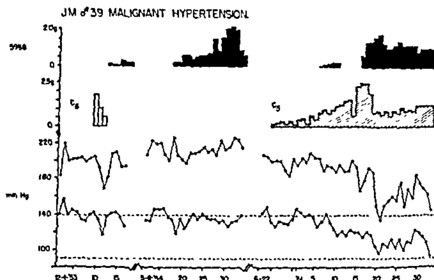


Fig. 32. Example of logic of using both ganglionic blockade and hydralazine (5968). Neither drug was effective alone in large doses. [illegible] in hospital and all readings are shown. Obviously, in this azotemic patient (NPN 76) with heart failure, death would have been the outcome had only one drug been used or had both been given in inadequate doses.

tients who do least well on combined therapy are usually men in the sixth decade with atherosclerosis, and not, as might be expected, those in malignant stages. Certain individuals, however, because of a too early reduction in dosage or because of a dosage schedule sufficient for the hospital but insufficient for the stresses of active living, continually show hypertensive levels, reaching as high as 180 or even 200 mm. Hg systolic during one of the five measurements a day. Several choices are open. a) The dose of one agent is increased for a month. If not successful, the dose of the other agent is increased. b) Protoveratrine in amounts insufficient to cause nausea is begun. c) Dietary salt is re-

stricted moderately. d) The patient is readmitted to the hospital and restabilized. e) Pheochromocytoma is suspected in patients whose blood pressures fluctuate widely and cannot be controlled. Reduction in dosage is not possible for those who keep themselves moderately hypertensive, even after 3 years. Those who do best are those who attain and maintain normotension (Fig. 33) (406).

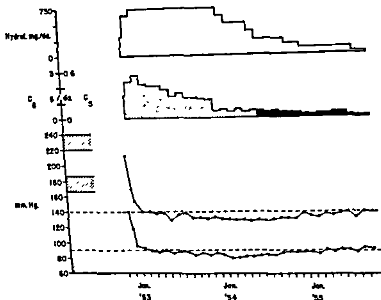


Fig. 33 Blood pressure and oral medication for a 34-year-old white male with malignant stage of hypertension. The range of pre treatment blood pressure is indicated by cross-hatching. The bar graphs indicate the drug intake, the open area representing hydralazine, the dotted hexamethonium (C_6), and the solid pentolinium (C_5). Note that the scale is different for the two methonium *compounds* since the second is approximately five times more potent than the first. (From Perry, H M, Jr, and Schroeder, H. A.: *Circulation*, *13* 528, 1956)

RESULTS EXPECTED

Since this monograph is not primarily concerned with a report on the results of therapy, only a brief resume of what can be expected with adequate therapy can be given. The long term effects have been published (401-403, 93, 168, 405-419). In general, those which could be predicted from an understanding of the disease occur; several unexpected and unpredicted effects appeared as well.

1. a) Heart failure due to left ventricular strain, which accounts for over 50 per cent of the death rate, is virtually

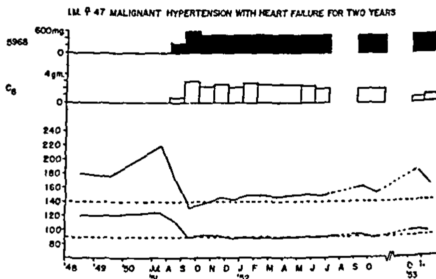


FIG. 34. One of the first four patients to receive ganglionic blockade (hexamethonium, C_6) and hydralazine (5968). Severe left and moder- fundi diet abits, omitted her drugs from time to time, began to complain of dyspnea, and hemorrhages reappeared in the ocular fundi. Hypertension was later controlled on larger doses of drugs and she remained symptom-free. From being invalided, she has been able to work full time in her own restaurant for five years, as long as she keeps her blood pressure down.

abolished, this within a few days. Salt can be added to the diet in from 2 to 6 months time. Also in a few weeks, digitalis can be eliminated (Fig. 34). Only a rare individual continues to require digitalis and dietary restriction of salt. We presume that these patients suffer from myocardial fibrosis due to atherosclerosis. Heart failure with only a moderate hypertension and much coronary arterial disease, however, is only moderately affected.

1. b) Abnormal electrocardiographic patterns indicative of left ventricular strain revert to normal within several months. Patterns suggestive of left ventricular hypertrophy revert to normal in some, but not in all cases. This may take 1 to 4 years. Enlarged hearts often, but not always, become smaller in roentgenograms. Time, 1 to 5 years (406).

2. a) A few weeks after the start of therapy the progression of renal damage due to arteriolar nephrosclerosis is halted. Unpredicted was a gradual return of depressed renal function in many, but not all cases. This occurs in from 1 to 4 years (405).

2. b) In from 1 to 6 weeks albuminuria diminishes or disappears. When caused by pre-existing organic renal disease, it remains at lessened quantities.

2. c) In azotemic individuals, nitrogen retention remains static or diminishes, unless initial values are over about 60 mg. per 100 ml. of nonprotein nitrogen in the blood. (Somogyi-zinc precipitate, corresponding to 75 to 90 mg. per cent by the phosphotungstic acid precipitate method.) Time, weeks or months. In those with higher values, azotemia usually, but not always, progresses to uremia; rarely, however, we have seen relatively acute elevations to 130 to 160 mg. per cent return to much lower levels. This may occur after 3 weeks or more (Fig. 35, 36).

2. d) Ocular fundi revert to normal. Hemorrhages are

RESULTS EXPECTED

Since this monograph is not primarily concerned with a report on the results of therapy, only a brief resume of what can be expected with adequate therapy can be given. The long term effects have been published (401-403, 93, 168, 405-419). In general, those which could be predicted from an understanding of the disease occur; several unexpected and unpredicted effects appeared as well.

1. a) Heart failure due to left ventricular strain, which accounts for over 50 per cent of the death rate, is virtually

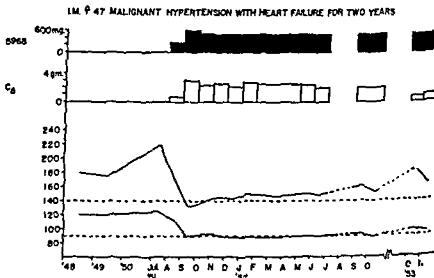


Fig. 34. One of the first four patients to receive ganglionic blockade (hexamethonium, C_6) and hydralazine (5968). Severe left and moderate right-sided heart failure disappeared in three days, grade IV fundi regressed, digitalis was discontinued, and salt was added to her diet (in November, 1951). She subsequently became sloppy in her habits, omitted her drugs from time to time, began to complain of dyspnea, and hemorrhages reappeared in the ocular fundi. Hypertension was later controlled on larger doses of drugs and she remained symptom-free. From being invalided, she has been able to work full time in her own restaurant for five years, as long as she keeps her blood pressure down.

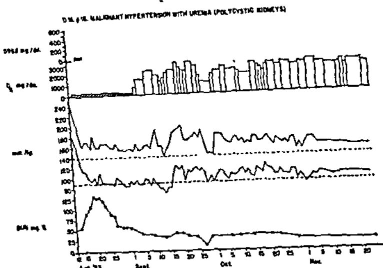


FIG 36. Medication, blood pressure, and nitrogen retention during hospitalization. The solid bars represent oral hydralazine (5968). The cross hatched bars represent parenteral and the open bars oral hexamethonium chloride (C_6). The parenteral dose has been multiplied by 10 in order partially to compensate for the much greater efficacy of this route of administration. Each of the points on the blood pressure curve is the average of at least six, and initially as many as 24, determinations All were made with the patient supine Note that azotemia is shown in terms of blood urea nitrogen rather than total nonprotein nitrogen

Except for life long enuresis, this 18-year-old white male was entirely well until 3 days before he entered the hospital. His mother had died with polycystic kidneys Pyrexia and malaise were the initial symptoms followed by lethargy, emesis, disorientation, and coma. Physical examination revealed in addition papilledema, hemorrhagic retinitis, minimal cardiomegaly and a pre-systolic gallop Roentgenologic examination suggested polycystic kidneys and 3 plus albuminuria was found After returning home the patient did very well. He was working when last seen in July, 1955, at which time his physical examination, including *fundoscopic* examination, was normal. His urine contained *no protein*. His antihypertensive regimen called for a maximum dose of 750 mg oral hexamethonium chloride and a constant dose of 100 mg of hydralazine every four hours. His sitting blood pressure at home averaged 160/80 *mm*. Hg. (From Perry, H M, Jr, and Schroeder, H. A.: *Circulation*, *14*·105, 1956.)

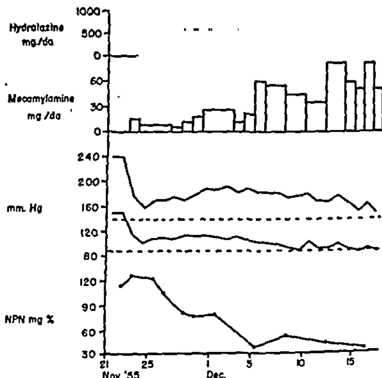


FIG. 35. Medication, blood pressure, and nitrogen retention during hospitalization. The solid bars represent oral hydralazine. The open bars represent oral mecamylamine (Inversine, Sharp & Dohme). Each of the points on blood pressure curve is the average of at least six, and initially as many as 24, determinations. All were made with the patient supine. In addition to the medication shown, 513 mg. of intramuscular hexamethonium chloride were administered on November 22 without any effect on the blood pressure.

Ex[illegible] ears previously, followed by th[illegible] 45-year-old Negro policeman [illegible] months before he entered Barnes Hospital. His initial complaints were progressive asthenia and increasingly frequent periods of syncope associated with vertigo and amblyopia. Urinary frequency and dyspnea appeared somewhat later; finally nausea and vomiting became frequent. There was hemorrhagic retinitis with bilateral papilledema and cardiomegaly. Although cardiomegaly was present, the lung fields were clear to percussion and auscultation and there was no edema. There was cylindruria and 3 plus albuminuria; only 100 ml. of blood contained 10 gm. of hemoglobin. Both electrocardiograms and roentgenograms of the chest indicated left ventricular enlargement. The decrease in azotemia and blood pressure following the institution of oral mecamylamine and hydralazine therapy is indicated in the graph. This man was discharged from the hospital with a regular diet without digitalis and with no symptoms except amblyopia referable to his hypertension or to his therapy, returning to work 3 weeks later. (From Perry, H. M., Jr., and Schroeder, H. A.: *Circulation, 14*:105, 1956.)

absorbed in 2 to 6 weeks, soft cotton wool exudates disappear in 1 to 4 weeks, papilledema slowly regresses in 4 to 12 weeks, and hard, waxy exudates and scars shrink to nothing in 1 to 3 years.

3. a) Atherosclerotic complications are less frequent. In from 1 to 6 weeks angina pectoris usually disappears, although rarely it becomes initially worse.

3. b) The incidence of coronary occlusion appears somewhat lower (after 3 to 5 years), although this disease ac-

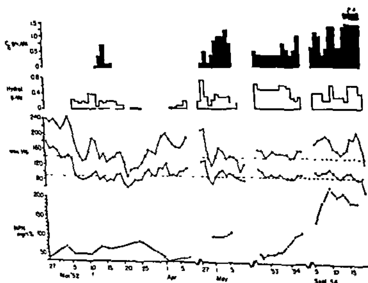


FIG 37. ... pertensio ... been stat ... full ...

... status or improved slightly; weight and health have increased. Lower: That of L. T., a 48-year-old man improved at first but azotemia later rapidly progressed to death. Pyelonephritis was found at autopsy; the kidneys together weighed 105 Gm.

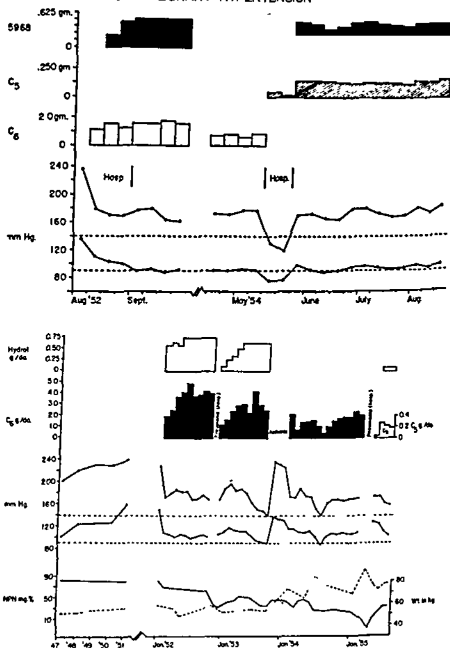

G.B. ♂ 52. MALIGNANT HYPERTENSION
.625 gm.
5968
0
.250 gm.
C_5
0
2.0 gm.
C_6
0
240
200
160
mm Hg.
120
80
Hosp.
Hosp.
Aug '52
Sept.
May '54
June
July
Aug.
0.75
Hydral g./da.
0.50
0.25
0
50
40
30
20
C_5 g./da.
10
0
0.4
0.2 C_5 g./da.
0
240
200
mm Hg.
160
120
80
90
NPN mg.%
50
10
80
60
40
Wt. in kg.
47
'48
'49
'50
'51
Jan '52
Jan '53
Jan '54
Jan '55

FIG. 37.

absorbed in 2 to 6 weeks, soft cotton wool exudates disappear in 1 to 4 weeks, papilledema slowly regresses in 4 to 12 weeks, and hard, waxy exudates and scars shrink to nothing in 1 to 3 years.

3. a) Atherosclerotic complications are less frequent. In from 1 to 6 weeks angina pectoris usually disappears, although rarely it becomes initially worse.

3. b) The incidence of coronary occlusion appears somewhat lower (after 3 to 5 years), although this disease ac-

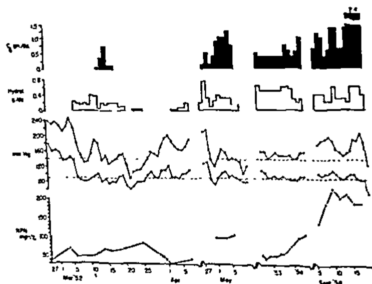


FIG. 37. Two directions of progress in azotemia and malignant hypertension. Upper: The condition of G. B., a 54-year-old man, has been static or improving slowly and he has been able to [illegible] full occupation [illegible] fair in [illegible] 72 mg. [illegible] remained [illegible] static or improved slightly; weight and health have increased. Lower: That of L. T., a 48-year-old man improved at first but azotemia later rapidly progressed to death. Pyelonephritis was found at autopsy; the kidneys together weighed 105 Gm.

counts for a major part of the mortality in treated patients.

3. c) In 3 to 5 years the incidence of cerebral hemorrhage is markedly lessened in those patients who have suffered one attack.

3. d) Also in 3 to 5 years the incidence of cerebral thrombosis is considerably lowered, but by no means abolished.

4. a) In patients for whom treatment is considered mandatory, continuation causes increased life expectancy while discontinuation results in early death (Fig. 37).

4. b) When a patient has survived 6 months of therapy, his chances of surviving 5 years are excellent.

Surgery: This monograph is not the place to discuss the pros and cons of surgical sympathectomy, an operation which has definitely altered the outcome and prolonged the life of many patients (420, 421). In our experience, drugs faithfully taken and properly administered have been of considerably greater value than surgical sympathectomy for the following reasons: 1. Cases too far advanced for surgery and unoperable cases with azotemia can often be salvaged. 2. All patients can be treated, regardless of the stage or degree of vascular damage. 3. Failures after surgical sympathectomy can be salvaged when hypertension has recurred and become severe. 4. The mortality rates of the most severe cases is considerably less than those following operation.

In actual practice, no patient should be denied the choice of drugs or surgical operation when hypertension is doing harm. When a patient is unwilling or unable to take drugs regularly, surgery should be urged in suitable cases. We must remember, however, that surgical sympathectomy, even the subtotal variety, can never block as many nerves as does adequate ganglionic blockade. Therefore, in cases resistant to ganglionic blockade surgical intervention can be expected to fail; contrariwise, cases re-

sponding well to ganglionic blockade alone can be expected to respond to surgery, even though the usual lumbodorsal sympathectomy only removes 50 to 60 per cent of the nerves. Operation therefore does not become the method of choice when medical measures fail, for the opposite holds true; i.e., drugs will work when surgery has failed. The one advantage of surgical over chemical sympathectomy is the lack of bother to the patient when the result is successful.

According to the data of White (421), when cardiovascular complications occur in hypertensive patients, the mortality is high. Left ventricular weakness and failure, cerebrovascular accidents, angina pectoris and myocardial infarctions cause a 3-year mortality rate of 82 per cent and a 10-year mortality rate of 96 per cent, with a mean survival time of 4.1 years. Surgical sympathectomy alters the 3-year rate to 24 per cent and the 10-year rate to 50 per cent, with a mean survival time of 6.1 years for the deceased

TABLE L

MORTALITY RATES AT FOUR YEARS OF PATIENTS SUBJECTED TO SURGICAL SYMPATHECTOMY, USUAL MEDICAL MEASURES, AND CHEMOTHERAPY (PER CENT)

Smithwick Group	*Smithwick's Series (420) Av Ages 38–47*		*White's Series (421) Ages 30–60*		*Author's Series* Ages 34–76 Chemotherapy*	
	Medical	*Surgical*	*Medical*	*Surgical*	*Stopped*	*Continued*
I	10	3				
II	33	12			—	0
III	58	19	84	24	32	1
IV	87	52			38	3
Azotemia	(100)	†	(100)	†	100	20
					100	45

* Most patients were 40–60.

† Not suitable for operation because of high operative mortality.

patients. Chemotherapy properly maintained definitely decreases the mortality rate in 4 years to a point well below these figures (Table L).

Nephrectomy also can alter the course of hypertension when 1) unilateral renal disease is present, 2) hypertension is early and not far advanced, and 3) the function of the opposite kidney is excellent. When the hypertension has produced arteriolar nephrosclerosis in the good kidney, removal of the offending one will naturally not result in "cure." Cases favorable for nephrectomy are rare.*

Bilateral adrenalectomy is indicated only in cases exhibiting evidences of adrenal cortical hyperfunction. Better diagnostic methods for overproduction of specific steroids may allow better selection for surgical therapy.

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* When any surgical operations are indicated, patients long treated by drugs will usually respond by strict normotension without drugs for one to two weeks, after which hypertension will recur. This phenomenon has also been seen after severe infections, gastro-enteritis and trauma. Apparently the ability of the peripheral vessels to respond to trauma is altered by these drugs for some days.

Chapter IX

A PRELIMINARY APPROACH TO THE TREATMENT OF ATHEROSCLEROSIS

OBVIOUSLY, control of a patient's hypertension will do no more than relieve cardiac strain, prevent further nephrosclerosis, prevent cerebral hemorrhage and relieve angina pectoris. Theoretically it will slow that part of the rate of progression of atherosclerosis which is dependant upon an elevated blood pressure. Since atherosclerosis is probably reversible (443), at least in so far as cholesterol-containing plaques are concerned (and possibly calcification (422)), treatment of the whole patient and his diseases becomes essential for prolongation of a life potentially shortened by cardiovascular damage. Therefore, an outline of the method we have used is given here; the method involves practical measures, based on theoretical approaches of most promise. Since it is most difficult to measure alterations in this disorder for the better or worse, until massive accidents occur, only time will tell if the results are favorable.

The serial measurement of lipoprotein fractions in blood is a procedure confined to the larger specialized centers. Total plasma cholesterol, however, is readily measured in most hospital laboratories. Based upon the assumption that lowered plasma cholesterol will in part prevent deposition of esters in plaques, one can attempt to lower these values by using some of the influences discussed in Chapter VII.

✓The method is based upon three influences: 1) removal of some trace metals; 2) a diet low in animal fats but containing adequate vegetable fats, particularly linolenate, and 3) the provision of an adequate amount of pyridoxine. For it is the possible effect of these biochemically and metabolically interrelated substances which can contribute to the disease (446).

METHOD

I. Diet: As discussed in Chapter VII, the most important factor in the development of atherosclerosis probably lies

TABLE LI

List of Foods to Be Avoided as Having a High Saturated, Low Unsaturated Fatty Acid Content (348)

Food	*Reason for Avoidance*
Fats	
Coconut	Short chain saturated
Margarine	Hydrogenated vegetable oils
Palm	Short chain saturated
Cocoa	Short chain saturated
Hydrogenated vegetable oils and frying fats	Long chain saturated
Lard, tallow	Long chain saturated
Butter, cream, cheese, whole milk	Short chain saturated
Hydrogenated peanut butter	Long chain saturated
Proteins	
Pork and pork products	Mainly saturated
Fat meats*	Mainly saturated
Sweetbreads	Not investigated
Domestic goose and duck	Fattened, not investigated
Processed meats of all kinds	Contain much fat
Hamburgers	Contain much fat

Note: The Pure Food and Drug Administration requires that all processed foods be labeled correctly. The labels should be read and those foods containing "hydrogenated shortening," "hydrogenated vegetable shortenings" or "pure meat products" should be avoided.

* The fat meats are beef rib roast, corned beef and tongue, lamb loin and shoulder, and mutton.

in the kind of fat in the American and European diet. From 30 to 40 per cent of the caloric intake comes from fat, mainly of animal origin. The purpose of the diet therefore is to restrict animal fat and hydrogenated vegetable oils and to provide an adequate intake of unsaturated vegetable fats containing linolenic acid. The basic rules are:

A. No obvious fat of animal origin should be eaten. Modern methods of fattening cattle for slaughter make a saturated body fat.

B. No hydrogenated vegetable oils should be used, since hydrogenation saturates an unsaturated fatty acid (Table LI).

C. Natural fat of vegetable origin containing the higher unsaturated fatty acids can be eaten in amounts as large as practicable, since these contain the essential unsaturated fatty acids linolenic and linoleic.

D. In general, reduce the fat content of the diet to about 20 per cent of the caloric intake.

The most available sources of essential fatty acids are in soy bean and corn oil, with the following iodine numbers:

	Iodine No	*Remarks*
Soy bean oil	130	Contains 11% linolenate
Corn oil	115	Contains 0.5% linolenate
Cottonseed oil	105	Contains no linolenate
Sesame oil	103	Contains no linolenate
Peanut oil	85	Atherogenic in animals

In order to obtain enough protein without animal fats, the following are recommended:

All kinds of fish and shellfish. Fish oils have a high iodine number.

Poultry and game, avoiding the fat (except domestic goose and duck). Chicken fat is high in linoleate.

Lean beef, lamb, and veal. Most animal fat is low in

linoleate and linolenate. There is fat in muscle fibres of cattle force fed on corn before slaughtering.

Legumes, such as peas, beans, lima beans, soy beans and its products. Their fats are largely unsaturated.

Skim milk and fat-free buttermilk. Butter, cheese, cream and whole milk contain principally short-chain saturated fatty acids; butter raises plasma cholesterol.

Cereals.

Some breads use hydrogenated vegetable oils for shortening.

Eggs. Yolks are fatty. Fry or scramble in soy bean oil.

Meat soups, only if all fat is skimmed off at icebox temperature.

Most canned soups contain butter, cream, or fat.

Salad dressings made of soy bean oil.

All nuts, especially walnuts. Seed oils contain unsaturated fatty acids.

Curd cottage cheese and other fat-free cheeses.

The two vegetable oils should be used for shortening. Deep frying should be done only in corn or preferably soy bean oil.

II. Vitamins: The second point of attack lies in the daily use of pyridoxine or pyridoxal, deficiency of which has caused the early lesions of atherosclerosis in animals, and which is low in many processed foods. About 5 to 10 mg. *per day is more than adequate.*

III. Trace Metals: Excessive amounts of certain trace metals in American human tissues may be concerned in cholesterol formation or the metabolism of fats. One tablet, 0.5 Gm., of Calcium Versenate (EDTA) twice a day, or another similar compound, may chelate and remove these metals. In some people, this substance alone will lower the cholesterol level in blood (Table LII).

Calcium: If calcium deposits are demonstrable in blood

TABLE LII

CHANGE IN PLASMA CHOLESTEROL WITH ORAL EDTA (1.0 GM./DAY)

Patients	*Sex*	*Age*	*Control* (mg %)	*Change* (mg %)	*Interval* (weeks)	*Major Diagnosis*
W H.	♂	54	293	−154	20	Angina pectoris
B. McD	♂	54	278	−150	35	Peripheral vascular disease
I S.	♀	70	276	− 40	4	Arterial hypertension
E. B.	♂	62	255	− 58	16	Coronary occlusion, convalescent
G H.	♂	45	252	− 36	25	Angina pectoris
G S.	♀	49	237	− 37	14	Arterial hypertension
E. S.	♂	77	225	− 74	3	Arterial hypertension
E. S.	♂	48	210	+ 18	44	Angina pectoris
H D	♂	63	189	− 49	8	Angina pectoris
R. S.	♂	54	177	− 38	12	Angina pectoris
J B.	♀	59	178	+ 16	4	Arterial hypertension
Mean			233	− 33		

vessels and symptoms or signs are present, the method of Clarke, Clarke and Mosher for removing metastatic calcium may be used (422). Trisodium EDTA, 5.0 Gm. in 500 ml. 5 per cent glucose solution is slowly infused intravenously over 2 to 6 hours. The patient is taught to slow the infusion at the appearance of unusual symptoms. Strangely enough, hypocalcemic tetany does not appear under these precautions. Ionized calcium salts and calcium chelated to proteins and peptides at a weaker stability constant than 10.6 (Log K_2 EDTA) are probably removed; the strongly chelated calcium in bone is probably not.

An injection is given daily for 5 days, 2 days are allowed for rest, and the 5-day course repeated. After a month or more for evaluation of symptoms, a second 50 Gm. is administered.

RESULTS EXPECTED

In Table LII are shown changes in blood cholesterol levels using calcium disodium ethylenediamine tetra-acetate (Calcium Versenate) in doses of 1.0 Gm. per day. In Table LIII are shown the changes produced by this agent

TABLE LIII

Effect of Regimen on Plasma Cholesterol (mg. %)

Patient	Age Sex	Pre-treatment Range		Pre-treatment Mean	No. Samples	2 Mo.	4 Mo.	Range After 3 Mo.	No. Samples	Diagnosis and Remarks
H. Sch.	49 ♂	237	244	240	2	146	168	146–172	12	Normal
E Stu.	70 ♀	276	278	277	2	151	216	216–227	12	Atherosclerosis
C. Cru.	62 ♂	260	300	280	3	236	200	112–237	9	Hypertension
S. Mat.	61 ♀	207	240	224	2	146	198	190–234	6	Hypertension
K. Sch.	59 ♂	200	217	212	4	120	141	117–154	8	Hypertension
G. Nes.	45 ♂	213	234	223	4	178	180	159–197	7	Hypertension
D. Blu.	49 ♂	219	295	244	4	179	204	176–204	6	Hypertension
G Boa	55 ♂	233	272	261	4	155	137	137–272	6	Hypertension and Atherosclerosis
B. McD.	52 ♂	204	278	241	2	145	128	105–156	8	Peripheral Vascular Disease
C Gri	57 ♂	210	253	234	3	206	181	171–201	6	Hypertension and Leriche's Syndrome
A. Han	60 ♀	174	207	194	3	168	171	171–200	5	Mild Hypertension
E. Fri.	69 ♀	217	231	224	2	128	185	161–196	3	Hypertension
E Shr.	49 ♂	228	249	239	3	119	232	119–232	4	Angina Pectoris
M. Bro	72 ♀	245	276	257	4	237	172	172–184	3	Atherosclerosis
L Bat.	62 ♀	256	300	280	3	183	250	241–250	7	Atherosclerosis
R. She	55 ♂	162	176	170	5	121	131	114–140	8	Mild Hypertension
D Lk.	56 ♀	481	624	552	6	377	366	366–422	3	Xanthomatosis
A Bla.	48 ♂	162	259	209	4	216	287		4	Hypertension
G Hir	46 ♂	238	262	250	3	185			1	Angina Pectoris
R. Ber	53 ♀	299	323	312	2	279	298	298–321	4	Hypercholesterolemia
Mean				258		181	200			

with diet and vitamin B_6 added. In general, the cholesterol changes are downward, although in some cases they are resistant to all three forms of therapy. Some depressed values did not rise when EDTA was discontinued, an expected result if trace metals were being removed.

All patients with angina pectoris were relieved of attacks of pain either completely or partly in that they occurred less than once a month. No electrocardiographic changes in the direction of normal were observed. No signs of hepatocellular damage developed.

Comment: While untried for periods long enough to evaluate these results on the disease, there is little doubt that cholesterol values can become quite low by this form of treatment. Changes in the degree of atherosclerosis are difficult to measure, but rough estimates of improvement in the disease can be estimated, especially when it has advanced far enough to give local ischemic symptoms. In the coronary arteries, relief of angina pectoris, if it is real and not imaginary, suggests resorption of plaques. In the aorta, lessening of the widened pulse pressure suggests a return of aortic elasticity. In the legs, relief of claudication indicates improvement in blood flow. In the cerebral area, abolition of minor paraesthesias and paralytic episodes indicates reabsorption of plaques. Some changes may be expected in time, except for a return of aortic elasticity.

Therefore, if degenerative cardiovascular disease is to be treated, as [illegible]
be altered [illegible]
health of v [illegible]

Chapter X

SUMMARY AND INTERPRETATIONS

NATURE is not prodigal with biologic functions othei than those for reproduction. Metabolic processes may have one or two alternate routes, but Nature does not provide dozens of methods by which defenses of a single function are maintained, by which digestion and combustion of a single substance proceeds, or by which *homeostasis is maintained. When an alternate pathway*, such as an anaerobic one, is substituted for an oxidation, malignant growth may result. It is proper, therefore, to look at the many and complex mechanisms which Man in his erratic searchings has partly uncovered, and try to unify them toward simplicity in an imitation of Nature. To do this we must depend upon evidence, in part factual and in part theoretical, delving into chemical causes.

Psychosomatic: While the psyche may affect the soma, the reverse is also true. Realization that some areas of cerebral function may depend upon the valence of *nitrogen* in certain configurations, that one primary amine mediates one area of the brain and another can affect another, and *that the anatomic chemistry of phospholipids* may influence healthy function, has opened up a wide field of investigation into the causes of mental derangements.

The psychic manifestations of arterial hypertension, when not due to organic cerebral vascular disease, are best explained by the effects of primary amines produced by intermittently or permanently ischemic kidneys. These

manifestations include emotional tension, anxiety, excessive drive, nervousness and the diencephalic blush. The blush is induced by histamine and resembles that seen with excessive quantities of circulating serotonin; tension, nervousness, anxiety result in some individuals from epinephrine, isoamylamine, tyramine and those synthetic or natural methylated analogues which inhibit cerebral monamine oxidase (ephedrine, amphetamine, etc.), thus preventing oxidative deamination of naturally occurring substances.

From the huge amounts of "tranquillizers" sold the American public, one might believe that chemically mediated nervous disorders were almost a national disorder. That many individuals might be so affected could be inferred from the abnormal trace metal content of American tissues; if one interfered with vanadium or monamine oxidase, or there was deficiency of vanadium, primary amines could be implicated as causes of a widespread cerebral disorder.

Hereditary: The ability to react to stress by vasospasm is an hereditary trait, apparently transmitted as a Mendelian dominant.

Neurogenic: The sympathetic nervous system is overactive, most likely because of increased cortico-hypothalamic activity. The posterior hypothalamus, for which serotonin has a predilection, is apparently stimulated more than is the anterior, the chemical mediator of which is not known. Cortico-hypothalamic activity is increased as a result of somatically formed primary amines. Neurogenic vasospasm causes neurogenic renal ischemia.

Renal: Renal disturbances dependent upon ischemia produce humoral vasoconstrictor substances. Trace metals, both normal and abnormal, are involved. Two metabolic pathways may be considered.

I. Anatomic causes of ischemia usually depend upon intrarenal parenchymal disease, atherosclerotic narrowing of renal arteries, or arterial and arteriolar nephrosclerosis secondary to hypertension. When the ability to react to stress by vasospasm is combined in one individual with organic renal ischemia, hypertension becomes permanent. The first two renal disorders are anatomic accidents, the last is caused by hypertension.

Anatomic or intermittent functional ischemia produces enzymatic disturbances in the kidney. The expected biochemical alterations resulting are:

A. Reduction of oxidative deamination of amino acids capable of anaerobic decarboxylation. The results in the kidney:
   a) Less urinary ammonia formed per mol of bicarbonate (theoretical). Ammonia from glutamine, however, would continue to be formed anaerobically.
   b) A change of pH in the cortex to the acid direction (found).
   c) Substitution of sodium for ammonia *in order to maintain acid-base balance in tubule (theoretical*, but logically inferred).

The urinary results:
   a) Urinary NH_3/acid ratio reduced (found).
   b) Acid urine (usually found).
   c) Sodium loss (found).

The expected remote results:
   a) More primary amines in blood (found).
   b) Release of renin (found in acute states).
   c) Stimulation of the adrenal cortex to production of aldosterone, in an *attempt to prevent excessive* sodium loss (found). Animals (and human beings) might therefore eat a little more salt in order to compensate (found in rats).

B. Renin is released, possibly because of the acidity secondary to the lessened formation of ammonia (renin is extracted from kidney only at acid pH). This postulate is unproven and not too sound, but we have no better one. Renin comes from the superficial areas of the cortex of the kidney, which becomes markedly acid when the renal artery is constricted. Adjustments take place with time—several weeks.

Result:

a) Hypertensin (angiotonin) is formed in blood at first through the physical release of renin (found).

b) With time, renin itself is no longer released into blood, but continues to act *in situ* (not proven, but renin disappears from blood). Perhaps renin is slowly modified into a somewhat different proteolytic enzyme.

c) Hypertensin I, or its analogue, formed in kidney, inactive on blood vessels, becomes activated either 1) through decarboxylation, leaving an active terminal NH_2, the decarboxylase being in blood and kidney; or 2) through action of a specific peptidase splitting off one or two amino acids and leaving a terminal $-NH_2$. In this latter event, the peptidase would necessarily be a manganous enzyme. The second pathway is the more logical one, as peptidases are known and peptide decarboxylases are not. Ordinarily, in the absence of renal ischemia, the small amounts of renin released into the renal venous blood form hypertensin which is inactivated both in kidney and in blood. In renal ischemia, the shift of locus of catabolism of hypertensin is from kidney to peripheral vasculature (theoretical, but monamine oxidase acts on both hypertensin and pherentasin, both peptides, and it probably occurs in smooth muscle of blood vessels).

d) Pherentasin is actually human hypertensin II, the amino acid content of which could be expected to differ from that obtained from bovine, horse, or hog globulin (unproven but very likely).

II. Enzymatic disturbances somewhat different from those resulting from organic renal ischemia may be caused by the accumulation of abnormal trace metals, notably cadmium. Cadmium is a nephrotoxic substance. Mercury and cadmium are the only metals which can readily displace zinc on a specific chelate, being in the same periodic group, having the same coordination number and making the same shaped complex. The expected results on renal acid-base equilibrium:

A. Inhibition of carbonic anhydrase by displacement of zinc (probable but not proven):
   1. More acid in urine.
   2. More base needed to neutralize acid, i.e., ammonia or sodium.

B. Inhibition of decarboxylases by displacement of zinc *on pyridoxal enzymes, causing a local vitamin* B_6 deficiency (one decarboxylase known to be inhibited. Zinc displacement logical but unproven):
   1. Less decarboxylation of amino acids other than glutamine.
   2. Less primary amines formed.
   3. Less ammonia available for urine.
   4. *Sodium wastage.*

C. Inhibition of transaminase, a pyridoxal enzyme which probably contains a metal (unproven but possible):
   1. Less transamination from glycine, aspartic, glutamic and other amino acids as a source of urinary ammonia (transamination not proven to be a source of urinary ammonia).
   2. *Sodium wastage.*

D. Aminoaciduria (found) either because of process B or interference with tubular reabsorption by inhibition of a carrier metalloenzyme, probably containing zinc.

The net results would be cortical acidity, less urinary ammonia and sodium wastage, the same as those found in organic renal ischemia but appearing by somewhat different routes. Primary amines in blood, however, would not be elevated (Fig. 38).

(If cortical acidity is the stimulus for the action of renin, hypertensin I would be formed *in situ* and released into renal venous blood where it would be converted to hypertensin II (pherentasin) by action of a specific manganous peptidase. Thus both organic renal ischemia and cadmium can cause the same end results. Naturally, renal ischemia accompanying neurogenic or pherentasin vasoconstriction would call into action pathway I.

Therefore, trace metals can be involved in the hypothetical peptidase, probably manganous, which converts hypertensin I to hypertensin II, in monamine oxidase, which inactivates it, in the decarboxylases and amine oxidases which are concerned in the hypertensive state, and even in tyrosinase (copper) which can inactivate norepinephrine, epinephrine, hydroxytyramine and tyramine.)

Therapeutic Note: Drugs or procedures which block sympathetic nerve impulses will counteract only the neurogenic portion of hypertension. Drugs or procedures which a) act to dilate vascular smooth muscle, b) increase renal plasma flow, or c) inactivate hypertensin II or pherentasin, will counteract the nephrogenic portion of hypertension. All known inactivators are metal binding or chelating agents.

The actions of hydralazine are fourfold:

d) Pherentasin is actually human hypertensin II, the amino acid content of which could be expected to differ from that obtained from bovine, horse, or hog globulin (unproven but very likely).

II. *Enzymatic disturbances somewhat different from those resulting from organic renal ischemia may be caused by the accumulation of abnormal trace metals, notably cadmium.* Cadmium is a nephrotoxic substance. Mercury and cadmium are the only metals which can readily displace zinc on a specific chelate, being in the same periodic group, having the same coordination number and making the same shaped complex. The expected results on renal acid-base equilibrium:

A. Inhibition of carbonic anhydrase by displacement of zinc (probable but not proven):
   1. More acid in urine.
   2. More base needed to neutralize acid, i.e., ammonia or sodium.

B. *Inhibition of decarboxylases by displacement of zinc* on pyridoxal enzymes, causing a local vitamin B_6 deficiency (one decarboxylase known to be inhibited. Zinc displacement logical but unproven):
   1. Less decarboxylation of amino acids other than glutamine.
   2. Less primary amines formed.
   3. Less ammonia available for urine.
   4. Sodium wastage.

C. Inhibition of transaminase, a pyridoxal enzyme which probably contains a metal (unproven but possible):
   1. Less transamination from glycine, aspartic, glutamic and other amino acids as a source of urinary ammonia (transamination not proven to be a source of urinary ammonia).
   2. Sodium wastage.

1. Decarboxylase inhibition, with the result that renal amino acid metabolism is further suppressed, and therefore less primary amine is formed.

2. Monamine oxidase stimulation, with the result that those primary amines which are formed are oxidized more readily. These include pherentasin or hypertensin II.

3. Hypertensin and pherentasin are both directly inactivated, either through carbonyl linkage, or what is more probable, removal of a chelated trace metal necessary for the integrity of the peptides.

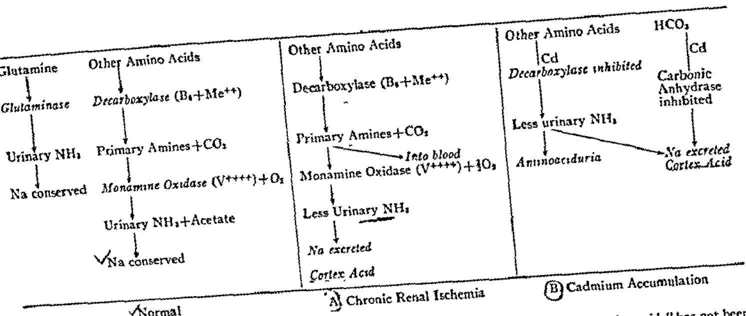
4. *Constricted* vascular smooth muscle is dilated, no matter what causes the constriction, by some unknown process which could be dependent either upon carbonyl or sulfhydryl binding or upon metal chelation.

In addition, histaminase is inhibited, a reaction common to many hydrazides

Adrenocortical: Renal sodium wastage (or need, as in heart failure) probably causes adrenal cortical production of aldosterone (theoretical but logical). This steroid probably sensitizes blood vessels to circulating vasoactive amines and sympathetic discharges, through intracellular sodium-potassium alterations (proven only for DOCA). Most cases of hypertension exhibit secondary aldosteronism because of renal sodium wastage.

Primary aldosteronism, by sensitizing vascular smooth muscle to normally circulating vasoactive amines and normal sympathetic tone, can produce a moderate degree of hypertension with normal renal plasma flow. Cases of this nature are not unusual. This type of hypertension, while benign, can slowly develop into a more serious variety with congestive heart failure the usual end result.

Therapeutic Note: While dietary salt restriction may induce enough sodium loss to negate the sensitizing effect of cortical steroids and salt on blood vessels, it stimulates



B_6 = Pyridoxal
Me^{++} = Metal
The reactions in italics have been demonstrated. Transamination to α ketoglutarate from "other amino acids" has not been shown for the sake of simplicity

Fig. 38. Proposed intermediary metabolism in ischemic and cadmium-loaded kidney.

(2) Cholesterol has a predilection for making unsaturated fatty acid esters. When insufficient unsaturated fatty acids are available for esterification, saturated fatty acids are used. These esters are quite insoluble and probably have lower specific gravities. Possibly breakdown, metabolism or excretion of cholesterol is more easily accomplished when esters are unsaturated than when made of saturated long chain fatty acids.

These two ideas are highly speculative. The mechanism of lowering plasma cholesterol by essential fatty acids is not understood.

Factors which may influence the deposition of cholesterol esters in sub-intimal spaces are:

C. *Physical*—Intra-arterial pressure, and changes of pressure (turbulence) at bifurcations of major vessels (Found).

D. *Metabolic*—Pyridoxal deficiency causes sub-intimal lesions identical microscopically to pre-atherosclerotic lesions observed in animals and man (Found).

a) Pyridoxal is necessary for the integrity of the mucopolysaccharides of sub-intimal ground substance (Inferred).

b) Pyridoxal affects fatty acid metabolism by promoting the synthesis of essential fatty acids from less unsaturated ones (Found).

c) Experimental pyridoxal deficiency and essential acid deficiency are quite similar in signs, differing only in a few basic enzymatic disturbances (Found). Vitamin B_6 will partly relieve essential fatty acid deficiency; essential fatty acids will partly relieve vitamin B_6 deficiency.

The biochemical interrelationships of three of these influences are:

1. Pyridoxal usually requires a metal for enzymatic activity. One abnormal metal (cadmium) can inhibit a pyridoxal metalloenzyme.

the adrenal zona glomerulosa to overactivity. The result: secondary hyperaldosteronism with salt depletion.

Atherosclerosis: Treated hypertensive patients no longer die of heart failure or renal failure when treated soon enough. They die of the effects of atherosclerosis. In order to prolong life, both blood pressure and blood lipids must be reduced.

Factors which may affect cholesterol synthesis or degradation and therefore atherosclerosis are:-

A. *Trace Metals:* 1) Chromium increases hepatic synthesis (in rats). Vanadium depresses hepatic synthesis. Manganese may be the normal metallic mediator of synthesis.

2) *EDTA lowers cholesterol levels in man moderately or markedly, almost surely by chelation and removal of a metal from an hepatic enzyme concerned in synthesis or catabolism.*

B. *Essential Fatty Acids: Fats containing linolenic acid (and possibly arachidonic acid) lower plasma cholesterol in man, even when given in excessive quantities.* Fats not containing linolenic acid raise plasma cholesterol. The mechanisms are not known but two can be hypothecated: (1) Squalene is a probable precursor of cholesterol. Squalene ($C_{30}H_{50}$) can be considered as a *highly* unsaturated C_{24} hydrocarbon chain, with 6 extra methyl side groups, and double bonds at the 2, 6, 10, 14, 18, and 22 positions or 4 carbon atoms apart. *Linolenic acid* (C_{18}) has double bonds at 9, 12, 15 positions, and arachidonic acid at *5, 8, 11, 14 positions, or 3 carbon atoms apart. It would be impossible to use any combination of ethylene groups from these two acids in the structure of squalene.* Degradation to acetate and subsequent synthesis would be required. No one knows much about this matter, except that squalene markedly accelerates synthesis of cholesterol.

application of therapy, present and to come. Rapid improvements are expected.

(1.) Reduce blood pressure of hypertensive patients to a mean level of 140/90 mm. Hg (or as low as tolerable) and keep it there indefinitely. Two drugs are usually necessary, given frequently, regularly and carefully; one should act on nerves and the other on vascular smooth muscle.

(2.) Lower plasma cholesterol to 120 to 160 mg. per 100 ml. (or about the same levels in mg. per cent as systolic pressure is in mm. Hg!). This can be accomplished slowly in some individuals, and soon will be in most by:

a) Metal chelation, probably removing from liver an abnormal trace metal affecting synthesis. Chelation and removal of metastatic calcium in blood vessels can probably be accomplished when desirable.

b) [illegible]et based on: Less total fat, to about 20 per cent of [illegible]ntake. Less animal fat, especially saturated fatty [illegible]eral, dairy products and pork are avoided. A[illegible]lenic acid (probably 0.5 Gm. per day is

[illegible]

[illegible] adequate. This coenzyme is given for logical, but untested reasons.

It is a long step from a lowered cholesterol to absorption of plaques, but the assumption is reasonable.

There are enough ideas now under experimental observation to strengthen the belief that atherosclerosis is a reversible disease, at least in so far as the fatty and calcific deposits are concerned. Arterial hypertension in man can be controlled indefinitely and sometimes reversed. Application of therapy to both diseases in the same individual may be expected to reverse in part the lethal and disabling effects of each.

2. Pyridoxal affects unsaturated acid synthesis, by promoting further desaturation to essential fatty acids (linoleic to arachidonic, linolenic to hexaenoic).

3. Pyridoxal lowers plasma cholesterol in monkeys deficient of this coenzyme and fed cholesterol.✓

4. Metals affect synthesis of cholesterol and fatty acids.

5. Removal of unknown metals lowers plasma cholesterol in man.

6. Feeding essential fatty acids lowers plasma cholesterol in man.

An hypothetical schema to include these influences is seen in Figure 39.

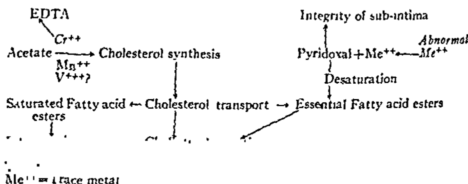


Fig. 39. Hypothetical interactions of metals, essential fatty acids and pyridoxal.

Therapeutic Note: Thus it would appear that therapeutic tools are now available to control or treat cardiovascular renal diseases quite specifically. While these tools represent first approximations, they are powerful enough and practical enough to be effective in any individual who wants to be treated and is willing to give the time and energy to do so. Since cardiovascular renal diseases account for over half the American death rate, considerable increase in our national longevity can be expected from wide

application of therapy, present and to come. Rapid improvements are expected.

(1) Reduce blood pressure of hypertensive patients to a mean level of 140/90 mm. Hg (or as low as tolerable) and keep it there indefinitely. Two drugs are usually necessary, given frequently, regularly and carefully; one should act on nerves and the other on vascular smooth muscle.

(2.) Lower plasma cholesterol to 120 to 160 mg. per 100 ml. (or about the same levels in mg. per cent as systolic pressure is in mm. Hg!). This can be accomplished slowly in some individuals, and soon will be in most by:

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c) Enough pyridoxine or pyridoxal. Probably 5 mg. per day is more than adequate. This coenzyme is given for logical, but untested reasons.

It is a long step from a lowered cholesterol to absorption of plaques, but the assumption is reasonable.

There are enough ideas now under experimental observation to strengthen the belief that atherosclerosis is a reversible disease, at least in so far as the fatty and calcific deposits are concerned. Arterial hypertension in man can be controlled indefinitely and sometimes reversed. Application of therapy to both diseases in the same individual may be expected to reverse in part the lethal and disabling effects of each

This book has attempted to give an orientation from biochemical abnormalities to clinical findings and specific therapy as the only satisfactory way to explain a disease and its control. As usual in scientific medicine, much more needs to be known than is known, but the directions for research are clear.

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INDEX

Alterations of the Vessel Wall: Injury to the endothelium of vessels favors coagulation of blood. This occurs much more commonly when the blood velocity is slow. Varicose veins and diseased arteries are more prone to thrombosis than are normal vessels.

Zeta Potential (14): Normally there is a difference in potential between the blood vessel wall and the center of the flowing stream of blood. It is probable that the vessel wall and elements of the blood are charged so that repulsion of the elements from the vessel wall occurs. When the blood vessel is damaged the potential is altered.

Biologicals and Foreign Substances (15): Certain substances, such as snake venom, are coagulants which favor arterial or venous thrombosis Foreign substances such as certain types of plastic prostheses favor coagulation. The incidence of thrombosis depends upon the plastic material which is employed. It should be recalled that plastics are prone to carry a large static electric charge. They differ in the amount and type of charge which they carry.

Temperature: Warming of the blood in some cases favors coagulation.

Cryoglobulins (16, 17, 18): There are certain globulins which coagulate at a relatively low temperature. When the globulins are present in the blood gangrene of the fingers and toes is common if the patient is exposed to cold Cryoglobulinemia is diagnosed easily by allowing a sample of blood to coagulate at room temperature, putting it in the bottom of a refrigerator and observing it after a few hours for a white flocculate.

Shape of Cells Cells of unusual shape, such as those of sickle cell anemia in which thread-like projections extend from their surface, tend to produce mechanical obstruction to vessels and then thrombus formation.

Age: The incidence of thrombosis increases with increasing age.

Malignancy: Carcinoma of the pancreas and lung as well as other malignancies are characterized by a high incidence of thrombosis (19).

Cardiovascular Disease: Cardiovascular disease producing congestive heart failure may produce stasis of blood in the lungs and

pulmonary thrombosis. Rheumatic mitral stenosis is especially prone to produce thrombosis of the pulmonary vessels due probably to pulmonary congestion and pulmonary artery disease. Heart disease associated with atrial fibrillation produces thrombosis probably due to stasis (20).

Heredity: Certain patients seem to have an hereditary tendency to thrombosis.

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Figure 292 William Harvey, 1578 to 1657. He comprehended the problem of the circulation of the blood and outlined the main factors of the circulation after performing a logically arranged and successfully executed series of experiments which lasted two years. He is considered to be the father of the experimental method.

CHAPTER 26

History

THE etiology, severity and location of disease of the vascular system usually can be deduced from a careful history. The patient should describe his symptoms after which specific questions should be asked concerning the arteries, veins, capillaries, lymphatics and other structures such as the nerves, bones and joints. Also questions concerning systemic disease (e.g., diabetes) should be asked.

General Data: The age, sex and race of the patient should be recorded in all cases. Certain diseases have a characteristic age distribution, such as arteriosclerosis which occurs commonly in the middle aged and elderly patients but is rare in the young. Other diseases have a sex predominance such as Raynaud's disease which is found almost entirely in the female. A racial predominance is found in some diseases such as sickle cell anemia which is found predominantly in the Negro.

Complaint and Present Illness: The symptom which prompts the patient to consult the doctor often is a key to the type and severity of peripheral vascular disease which is present. The presenting symptoms may be pain, tenderness, fatigue, cramps, ulceration, gangrene, edema, atrophy, numbness, burning, coldness, heat, black and blue spots, discolored areas, restless legs and prominent veins. These symptoms may be produced by disease of the arteries, veins, capillaries, lymphatics or other structures.

Past History: This is important in determining the time of onset of symptoms and may give a clue to the etiologic diagnosis. The past history should include a description of previous diseases, hospitalization, occupation, habits and drugs which have been taken.

Previous Diseases: The past diseases of importance are: polycythemia, anemia, frostbite, trench foot, immersion foot, chill-

blains, arthritis, diabetes, varicose veins, thrombophlebitis, syphilis, hypertension, coronary artery disease, infections such as tuberculosis, allergies, athlete's foot, vitamin deficiencies, eczema, malignancies, purpura, trichinosis and gout.

Previous Hospitalization: Questions concerning previous hospitalization may reveal a cause for symptoms. A past history of diabetes, syphilis, arteriosclerosis or accidents may provide clues to the cause of the present symptoms. A history of high blood cholesterol, abnormal glucose tolerance test, high blood uric acid, eosinophilia or other unusual laboratory findings may assist in establishing a diagnosis.

Occupation: The occupation may suggest an explanation for the symptoms. Battery makers may have plumbism which would explain the presence of night cramps. Bartenders may have alcoholism which would explain the presence of neuritis. Riveters may have pneumatic hammer disease which would explain Raynaud's phenomenon. A change in occupation may correlate with the onset of symptoms such as those associated with the scalenus anticus, cervical rib, hyperabduction, mal-position or costoclavicular syndromes.

Habits: The habits of the patient may be informative. Poor eating habits may result in nutritional neuritis. Excessive use of alcohol may lead to alcoholic neuritis. Excessive use of tobacco may aggravate an already existing organic arterial disease. Crutches or trusses may lead to arterial or venous obstruction.

Drugs: The drugs taken in the past should be recorded. An adequate intake of vitamins would suggest that vitamin deficiencies are not present. Ergot for the treatment of migraine suggests ergotism and may explain Raynaud's phenomenon. Sulfonamides taken for infections suggest the possibility of polyarteritis nodosa.

SYMPTOMS OF ARTERIAL DISEASE

The symptoms of arterial disease include pain, tenderness, sensory disturbances, cramps, restless legs, fatigue, temperature changes, color changes, ulceration, swelling, nail changes and atrophy.

Pain: The pain of arterial disease occurs: 1) with exercise; 2) at rest; 3) with elevation, or 4) with local heating of the ischemic part.

Pain With Exercise: This is characteristic of arterial insufficiency and may occur in the legs with or without palpable pedal pulses. Claudication may occur in the limbs from angiospasm after exercise. Claudication occurs also in the spinal cord and abdominal structures (vida infra).

Intermittent Claudication: Pain produced by exercise which disappears with rest is designated intermittent claudication. Arterial obstruction is almost always the cause Where the disease [illegible] g and dis- [illegible] or uphill [illegible] ground or walking slowly (18). Pain which lasts more than ten minutes after rest is suggestive of some other disease state such as pes planus or arthritis and is not typical of arterial disease. The pain of intermittent claudication probably results from stimulation of nerve endings by metabolites which are produced by muscular contraction (1, 2, 3). Normally these metabolites are oxidized or are carried away by the blood stream as fast as they are produced and they never attain sufficient concentration to cause irritation of nerve endings. In patients with obstructive arterial disease the metabolites cannot be carried away as rapidly as they are formed so that they reach a concentration which irritates the nerve endings sufficiently to cross the threshold of pain. With rest the excess metabolites are reduced and discomfort disappears. Boyd (4) has described three grades of intermittent claudication which are related to the amount of arterial disease which is present (figure 228).

Intermittent Claudication with Palpable Pulses· Patients with intermittent claudication usually have decreased or absent peripheral pulses at rest; however this is not true of patients who have disease in small arteries distal to large palpable arteries or of patients whose disease is in main arterial branches which are deep and are not accessible for examination by palpation. For example, intermittent claudication of the thigh occurs in patients with disease of the deep femoral artery often when the superficial

femoral artery is patent and the pedal pulses are good. Likewise peroneal artery obstruction may result in claudication involving the outer part of the leg yet the dorsalis pedis and posterior tibial arteries pulsate normally. Spinal and abdominal claudication (vida infra) may be present yet the peripheral arteries may pulsate normally.

Angiospastic Claudication: In patients with arterial disease exercise produces diminution of the peripheral pulses. With rest the pulses return. This phenomenon has been attributed to angiospasm (5). It is probable, however, that angiospasm is not the usual cause for this phenomenon but that the disappearance of the pulse may be due to mechanical obstruction of the arteries which limits the rate of arterial inflow at a time when blood is being rapidly pumped out of the limb through the veins. Also the pulses disappear with exercise before as well as after sympathectomy when an arterial obstruction is proximal to the part being examined. In addition, exercise of a limb results in vasodilatation which is greater in normal than in diseased areas. As a result there is shifting of blood toward the healthy areas and away from the diseased areas which results in decreased pulsations in the diseased part after exercise.

Spinal Claudication· Ischemia of the spinal cord after walking may result in pain in the legs and in transient spastic paraplegia which may be associated with the development of positive transient Babinski reflexes. Spinal claudication often is associated with occlusion of the lumbar arteries from arteriosclerosis or syphilis. Spinal claudication may be unilateral or bilateral and may occur in the presence of palpable peripheral arteries. Neurologic manifestations such as numbness, weakness, parasthesias, spasticity or anesthesia may occur on walking even short distances (20, 21).

Abdominal Claudication: Patients with occlusive arterial disease involving the intestinal branches of the abdominal aorta may have ischemia of the abdominal organs (6, 7, 8). This results in attacks of abdominal pain, cramps or dyspepsia which occur after exercise or at rest two to three hours after meals. Usually good peristalsis is present and there are no localizing signs. Such attacks may precede arterial thrombosis (9).

PAIN AT REST: Pain at rest may be due to ischemic neuritis,

chronic or acute arterial occlusive disease, ulceration or gangrene or over-dilatation of vessels. Disease states which are not associated with arterial obstruction such as erythermalgia may also produce pain at rest.

Ischemic Neuritis: This may produce mild or severe pain and may be associated with numbness, tingling, aching, burning, or tenderness. Ischemic neuritis is common with diabetes, thromboangiitis obliterans, arteriosclerosis obliterans and syphilis. The origin of the pain in each of these diseases is somewhat different. Diabetes produces ischemia of nerve trunks. In addition there is a primary deterioration of the nerves which is unrelated to the amount of arterial disease which is present. Often diabetic neuritis is present in the presence of normally pulsating dorsalis pedis and posterior tibial arteries. Diabetic neuritis in its early stage responds usually to the parenteral administration of large doses of vitamin B12 and B complex while the pure ischemic neuritis of arteriosclerosis obliterans usually does not respond well to these agents Thromboangiitis obliterans produces neuritis due to an inflammatory reaction involving nerve trunks. However true ischemic neuritis occurs as well and is associated with Wallerian degeneration of the nerves. Arteriosclerosis obliterans produces arterial insufficiency of vessels supplying the nerve trunks and causes a pure ischemic neuritis. Syphilis produces inflammatory reactions of the posterior nerve roots and ischemia of nerve trunks which results in neuritis and "lightning" pains in the limb.

Chronic Arterial Occlusive Disease: This produces pain at rest because of a breakdown of tissues which occurs usually when advanced arterial disease is present. The pain often is intense and burning and may be located around the nails or may involve the acral portions of the limbs. Elevation of the limb, heat and exercise aggravate the pain while dependency, coolness and rest decrease the pain. In the diseased limb with the leg elevated, blood flow is diminished because the force of gravity tends to decrease flow. With heat and exercise, pain is produced because the blood is shunted into healthy vessels which can dilate, thus depriving the area where diseased vessels are present (10). Usually the pain is associated with a dusky rubor which is a result of paralysis of blood vessels with capillary dilatation from hypoxia. The pres-

ence of rest pain is evidence that the blood flow is inadequate to meet the nutritional requirements of the resting limb.

Acute Arterial Obstruction: This is associated with pain at rest. When complete obstruction occurs from an embolus the onset of pain is sudden and is associated for a few hours with sensory disturbances of numbness, tingling and hyperesthesia after which anesthesia develops. Obstructions developing from inflammation of a vessel (temporal arteritis) are associated with marked tenderness of the vessel often with swelling.

Ulceration: Ulcers due to thromboangiitis obliterans produce severe pain when nerves are involved in the inflammatory process. In contrast, ulcers associated with arteriosclerotic obliterative disease usually are less painful.

Erythermalgia: This disease produces pain at rest especially when the skin is warm and is associated with over-dilatation of the blood vessels. Relief of pain may be obtained by cooling the feet which some patients accomplish by sleeping with the feet uncovered or near an open window.

PAIN DUE TO ELEVATION OF LIMBS: Elevation of the limbs in patients with arterial disease increases pain because of ischemia which occurs as a result of blood flowing against gravity. Often the flow is adequate for tissue needs when the limb is horizontal but inadequate when the limb is elevated. Dependency often results in temporary relief of pain; however, with continued dependency pain may return because of the formation of edema which compresses the capillaries and limits flow. Best relief of pain usually is obtained when periodic changes in position of the limb from horizontal to dependency are made. Elevation of the part decreases the pain of erythermalgia because here the overdistention of vessels which is characteristic of the disease and which causes pain is decreased.

PAIN DUE TO CHANGE IN ENVIRONMENTAL TEMPERATURE: A moderate temperature frequently is the most satisfactory environment for patients with arterial disease as it produces neither undue constriction nor dilatation of the vessels. Direct heating of an ischemic limb increases pain because of the increase in metabolism of the tissues produced by the heat. Heat also aggravates the pain of erythermalgia because it dilates vessels, while cooling

provides relief. Body chilling may result in arterial spasm which produces pain especially in patients with Raynaud's disease (vide infra). Here the cold part gives rise to symptoms of ischemia (numbness, tingling, pain, decreased sensation) which persist as long as the spasm persists.

Tenderness: This is characteristic of ischemic tissues especially if arterial insufficiency is severe. The tenderness often involves muscles and is not limited to a peripheral nerve trunk or its branches. The tenderness is increased after exercise, elevation or the direct application of heat. Tenderness over arteries occurs in thromboangiitis obliterans, temporal arteritis or periarteritis nodosa which is due in part to inflammation of the vessels. Tenderness occurs with attacks of intermittent claudication when *the patient continues to walk even though ischemic pain is present.* Tenderness also follows leg cramps which may or may not be associated with arterial disease.

Sensory Disturbances: Numbness, anesthesia, burning or tingling often are signs of arterial disease and occur when nerve trunks are involved in the disease process. An embolus to a small vessel also may produce numbness as an early sign. In the presence of arterial spasm (Raynaud's disease) anesthesia or pain results and disappears when the spasm is released. Tingling, numbness or burning in the upper extremity often is associated with a cervical rib, enlarged scalenus anticus muscle, crutch arteritis and frostbite.

Muscle Cramps: These may or may not be due to vascular disease They occur suddenly with tightness and spasm of a muscle group. The contraction lasts only a few minutes after which a sore spot may remain for minutes or days. Muscle cramps may occur during the night or day. Night cramps from arterial insufficiency may be due to altered cellular membranes with local electrolyte disturbances. If the cramps occur in a pulseless limb arterial disease usually is the cause. Ischemic cramps may be improved by lowering the feet below the level of the heart, improving the circulation with vasodilating drugs or surgery which increases the circulation to the limbs. Leg cramps may occur in normal individuals without vascular disease. Flat feet or poor posture result in straining of certain muscle groups of the leg dur-

ing the day with unequal rates of relaxation of the agonist and antagonist muscle groups at night which results in cramps Cramps of this type often are improved by arch supporters or by improving posture. Cramps may be secondary to nerve trunk or nerve root irritation such as those seen with arthritis of the spine or a ruptured intervertebral disc. Calcium lack, for example with hypoparathyroidism, is a rare cause. Alteration in potassium metabolism occurring in patients with diabetes being treated with insulin is associated with leg cramps. Chloride loss from diuretics, hot weather or heavy exercise results in cramps and may be improved with salt. Pregnancy is associated with leg cramps and is due at times to phosphorous excess which can be reduced by giving calcium, aluminum hydroxide and a low phosphorous diet. Edema of the tissues due to venous insufficiency or venous obstruction produces altered metabolism and night cramps. Most of the cramps discussed may be improved by decreasing muscle irritability by giving quinidine sulfate and diphenhydramine hydrochloride (Benadryl®). The treatment of night cramps depends upon the underlying disease state.

Restless Legs: These should be differentiated from muscle cramps. Restless legs are commonly seen in patients with arteriolitis such as with malignant hypertension with necrotizing arteriolitis The patients are unable to find a comfortable place for their legs and they turn and toss in bed. The diagnosis is made on the basis of a therapeutic test in which nitroglycerin provides relief.

Fatigue: Fatigue in the legs after walking is an early sign of vascular disease. Fatigue may be produced also by a short achilles tendon, flat feet, varicose veins, or other causes. Fatigue, however which comes on after walking one to two blocks at an average pace and which disappears in two or three minutes with rest suggests arterial insufficiency. Fatigue of the muscles on walking often is overlooked by the patient and physician although fatigue is a significant symptom of arterial disease.

Temperature of the Skin: This is altered by environment, metabolic disturbances and by functional or organic arterial disease (11, 12). Knowledge of the environmental temperature is important in evaluating the complaint of coldness or increased temperature of the extremities. In a comfortable environment (23

degrees C) most individuals have skin temperatures of the hands which are greater than those of the feet (13). In a warm environment (30 degrees C) the hands and feet are warm and approach equal temperatures. In a cold environment (19 degrees C) the hands and feet are cold and approach equal temperatures. Many variations of this average state of affairs exist. Considerable disease of the arteries may be present in the presence of warm extremities. For example, after sympathectomy of an ischemic limb which has a diminished blood flow the skin temperature often is warm. The skin temperature is increased by alcohol, mental rest, sleep, food and a warm environment (14, 15). The patient should be questioned concerning the temperature of the extremities during week-ends when at rest and during work days when anxiety may exist. Eating, especially of protein foods, increases the skin temperatures greatly. Metabolic disturbances, functional vascular disease and organic vascular disease alter the temperature of the limbs.

Metabolic Disturbances: Hypothyroidism is characterized by cool hands and feet and hyperthyroidism by warm hands and feet (12, 16). The thyroid abnormality may be primary or secondary due to disease of the pituitary gland. Adrenal medullary stimulation produces an increase in metabolism but cool extremities because of circulating epinephrine and nor-epinephrine.

Functional Vascular Disease Such as Raynaud's Disease: This produces intermittent attacks of cold fingers which last from ten minutes to an hour. The coldness is precipitated often by a cold environment. In many cases the attack may be reproduced by placing the hands in water 15 degrees C for fifteen minutes (see cold sensitivity test). The attacks are associated with color changes which involve some, but often not all of the digits. The coldness of the fingers is associated with tingling and numbness if arterial spasm is long lasting. Functional vascular disease is suspected when the patient complains of attacks of cold hands or feet of short duration after which the part becomes warm when in a warm environment or at night when resting in bed. Cold, wet extremities suggest a functional disturbance due to increased sympathetic vasoconstriction.

Organic Arterial Disease: This produces coldness of the extremities which is persistent without significant increases in temperature with rest in a warm environment. Aortic obstruction produces coldness of both feet and all toes, however the coldness is more pronounced when there is disease involving the peripheral arteries. With segmental aortic obstruction with patent small vessels there is usually sufficient collateral circulation to keep the feet warm. Coldness of one or two fingers is highly significant and usually indicates arterial obstruction involving small arteries Coldness of one hand suggests cervical rib, the anterior scalenus syndrome, ruptured cervical intervertebral disc, cervical arthritis, thromboangiitis obliterans or localized arterial disease. Arteriosclerosis may involve the arteries of the arms, but involves the legs more frequently. Thromboangiitis obliterans involves the arms more commonly.

Color of the Skin: Discoloration of the skin may be a presenting symptom. A waxy pallor is characteristic of arterial insufficiency. This color is seen during attacks of Raynaud's phenomenon or when ischemic limbs are elevated. A bright pink color is characteristic of erythermalgia. Cyanosis of the acral portion of the body is characteristic of acrocyanosis.

The color of the skin (white, pink or blue) is due mainly to the amount and color of the blood in the capillaries and subpapillary venous plexuses (17). The color of the blood in these vessels is determined by the rate of flow and the amount of dissociation of oxygen from the blood. Cyanosis of the skin indicates a sluggish or diminished skin blood flow. Local heat to a diseased limb may intensify the cyanosis because more oxygen is removed from warm than from cold blood. With normal blood flow through the skin at a comfortable temperature the blood is only slightly reduced and the skin color is pink. With arrest of the arterial circulation, as occurs after ligating an artery or elevating an ischemic leg, the skin is bloodless and the color of the skin depends upon the color of the tissues which normally is white. With partial arterial obstruction cyanosis is present due to retarded blood flow to the skin, and the skin is slightly blue. Still deeper cyanosis occurs with obstruction of the venous outflow as almost complete stasis of blood occurs.

Ulceration: Ulcers of the skin may be due to arterial, capillary, venous or extravascular disease. Arteriosclerosis obliterans and thromboangiitis obliterans produce obstruction of arteries including the small arteries of the leg or foot and produce ulcers of the tips of the toes or the dorsum of the foot. The ulcers may follow trauma or may occur spontaneously. Ulcers are common in diabetes, sickle cell anemia and in other disease states.

Swelling: This may occur with arterial insufficiency when capillaries are damaged and an increased capillary permeability exists. The swelling is aggravated by the dependent position and is improved by the horizontal position

Nail Changes: With arterial disease the toenails often become discolored, thickened and rigid. Fungus disease of the toe nails often is associated with peripheral arterial disease. The finger nails are curved longitudinally and tend to pull away from the nail bed with Raynaud's disease.

Atrophy: The skin becomes thin and shiny and the circumference of the limb decreases (muscle atrophy) in patients with arterial insufficiency.

SYMPTOMS OF VENOUS DISEASE

The symptoms of disease of veins are: pain, tenderness, swelling, ulceration, muscle cramps, varicosities, color changes of the skin, changes in temperature of the limb and sensory disturbances.

Pain: Pain on standing or on walking is present with deep vein thrombosis or with venous insufficiency and must be differentiated from intermittent claudication due to arterial disease. The pain of venous disease is not relieved completely in one to five minutes by standing quietly as is the pain of arterial insufficiency but continues as long as the patient is in the standing position. Characteristically, the pain is below the site of a venous obstruction and consists of a "bursting" sensation which is relieved by a long period of elevation of the limb (19).

Pain in the Abdomen or Pelvis: This may occur from thrombophlebitis and distention of pelvic veins and is described as an ache, pressure or fullness which is relieved by a few hours rest in bed in the pelvis-up head-down position. The pain is aggravated by standing or sitting.

Pain at Rest: The pain of acute thrombophlebitis is present at rest regardless of the position of the leg however it is improved somewhat with the limb elevated and is aggravated by dependency. It is severe in the region of the involved veins. The pain is improved by reducing the congestion with hot, wet packs.

Pain Due to Dependency of the Limb: Venous disease is aggravated by dependency. This is in contrast to arterial disease in which pain is improved with dependency. Dependency favors inflow of blood to the limb with capillary hypertension, congestion of the tissues and swelling while elevation promotes venous drainage and reduces congestion thereby relieving pain.

Tenderness: This is characteristic of patients with superficial or deep vein thrombophlebitis. If superficial veins are involved the tenderness occurs along the course of the veins. If deep veins are involved the muscles are tender which may be demonstrated by palpation or by passively dorsiflexing the foot which results in pain in the calf (Homan's sign).

Swelling: Deep venous obstruction or venous insufficiency characteristically produces swelling. Swelling occurs often around the ankle and foot and frequently is of the soft, pitting type. Swelling of long duration may result in thickening of the skin and fibrosis of the subcutaneous tissue which is associated with a non-pitting edema. The edema of venous obstruction increases usually during the day, is greater before retiring and is reduced after 8 hours in the horizontal position or after elevation of the limb for a few hours.

Ulceration: Ulcers of venous obstruction and venous insufficiency usually are associated with swelling and discoloration of the skin resulting from chronic stasis of blood in the tissues. Ulcerations due to venous disease often are on the inner aspect of the leg in its lower third just above the internal malleolus and vary in size from 1 to 20 cm in diameter.

Muscle Cramps: These are common with venous disease and are due to edema of the tissues. The cramps may be improved by correcting the abnormality of the veins, reducing the edema by wearing elastic bandages or by frequent elevation of the limb.

Fatigue: This is a sign of venous disease. It comes on after standing or walking and is due to congestion of the tissues. The

fatigue continues as long as the limbs are dependent and is improved by elevation.

Varicosities: These are tortuous, dilated veins which may or may not be associated with insufficiency of valves. Varicose veins in themselves without venous insufficiency or venous obstruction do not as a rule produce symptoms.

Color of the Skin: Obstruction of veins results in cyanosis due to distention of the capillaries and subpapillary venous plexuses, increased venous pressure, retarded blood velocity and over-reduction of hemoglobin. Improvement in color results from elevation of the part.

Temperature of the Skin: The temperature of the limb depends upon the nature of the disease. If acute thrombophlebitis is present the limb is often warm because of local inflammation (vasodilatation and increased metabolism) of the part. Occasionally the inflammatory process produces arterial constriction which decreases the temperature of the limb somewhat. After the acute phlebitic process has subsided, the local metabolic processes decrease but the arterial constriction may persist, producing a cool limb which may be below the temperature of the normal limb

Sensory Disturbances: Burning, tingling and itching occur with venous disease. A decrease in the sensitivity of the skin may occur after chronic venous obstruction when edema has been present for a long time, especially if tissue changes have taken place.

SYMPTOMS OF CAPILLARY DISEASE

Symptoms usually are related to: (1) increased capillary fragility, or (2) increased capillary permeability.

Increased Fragility: This is characterized by hemorrhage, echymosis or petechiae.

Hemorrhage: This is common with hypertension, idiopathic thrombocytopenic purpura (Werlhoff's disease) secondary thrombocytopenia, scurvy, liver disease, pseudohemophilia, senile purpura, toxic states, allergic states such as Henoch's or Schoenlein's purpura and hypoprothrombinemia. Hemorrhage may occur in the brain, eye, mouth, esophagus, stomach, duodenum, skin, joints, kidneys or other structures. The symptoms produced depend upon the structures involved.

Ecchymosis: The occurrence of "black and blue spots" is common with increased capillary fragility. Any of the diseases producing hemorrhage (vide supra) can produce ecchymoses. Ecchymoses may appear spontaneously or after trauma. The spots are at first red, then become blue as blood pigments change chemically. Ecchymoses may disappear entirely or leave brown pigmented spots on the skin.

Petechiae: These are caused by diseases which attack capillaries (diabetes, scurvey, allergic states, nephritis, toxic states, hypertension, Werlhoff's disease, subacute bacterial endocarditis, collagen diseases). Often they occur where hydrostatic pressure is high, for example about the ankles, or where localized capillary disease is present, for example, under the finger nails or in the conjunctiva. Petechiae in the skin, when numerous, produce itching or burning.

Increased Permeability: The usual manifestation of increased permeability is a swelling or hive which is similar to that produced by a bee sting. Increased permeability occurs with allergic states, serum sickness, toxic states, sepsis, scurvy and nephritis and with angioneurotic edema. The symptoms produced depend upon the structures involved, for example, dyspnea is produced when the edema involves the trachea or impaired vision occurs when the edema involves the eye.

SYMPTOMS OF LYMPHATIC DISEASE

The symptoms of lymphatic disease are swelling, pain, fatigue, increased temperature of the skin, tenderness, parasthesias, muscle cramps, color changes and ulceration of skin.

Swelling: Swelling is a primary complaint of lymphedema and often is the first symptom. The edema is of the non-pitting type. It is increased slightly by dependency but is not decreased significantly by a night's rest in the horizontal position. As the disease becomes chronic changes of position do not influence the size of the limb because of fibrosis of subcutaneous tissues.

Pain: Exercise or movement of a limb with acute lymphangitis characteristically produces pain. Pain is not typical of patients with chronic lymphatic disease, however in severe cases exercise may be difficult because of the increased bulk of the limb.

Pain at Rest: The pain of acute lymphangitis is located at the site of the inflammatory process along the course of the inflamed lymph vessels. The lymph nodes usually are tender. The pain disappears as the acute stage subsides and is substituted by a feeling of tightness and discomfort in the chronic stage.

Pain Due to the Position of the Limbs: With acute lymphangitis the pain is increased by dependency and improved by elevation. The pain is due to distention of the lymph vessels and tissues when the limb is in the dependent position. In the chronic stage the position of the foot does not influence the symptoms greatly.

Pain Due to Change in Environmental Temperature: The application of heat to the limb may provide some relief of pain in patients with acute lymphangitis but has little effect in the chronic forms.

Fatigue: This is a common complaint of patients with chronic lymphedema with congestion. Standing or walking produces a tight, tired feeling of the limb and a generalized fatigue which is associated with the moving of a large part of increased weight especially when the limb is greatly enlarged.

Temperature of the Limb: In acute lymphangitis the temperature of the limb is increased; however with chronic lymphedema the temperature usually is not abnormal.

Tenderness: This is characteristic of acute lymphangitis and it follows the course of the infection in the lymph vessels and extends to the lymph nodes which usually are more tender than the lymph vessels. Chronic lymphedema usually is not tender.

Paresthesias: Numbness, burning and tingling are common with acute lymphangitis but are not common in patients with chronic lymphedema.

Muscle Cramps: These occur because of congestion of the tissues and are improved by measures which reduce congestion.

Color Changes: With acute infectious lymphedema the skin is pink or red along the inflamed lymphatic vessels. In chronic lymphedema the color of the limb may be normal but with prolonged lymphatic stasis, dermatitis develops with discoloration.

Ulceration: Ulceration is not common in patients with lymphedema but may occur after trauma to lymphedematous areas.

SYMPTOMS PRODUCED BY NON-VASCULAR STRUCTURES

Diseases of various non-vascular structures produce symptoms which may be mistaken for symptoms of vascular disease. These include diseases of nerves, bones, joints and bursae, systemic disease, infections and diseases of the blood.

Diseases of the Nerves: Neuritis may occur from non-vascular causes for example various infections, poliomyelitis, syringomyelia, *tabes dorsalis*, *diabetes mellitus*, pernicious anemia, leprosy, gout, beriberi, lead poisoning, rheumatic fever and other causes. Peripheral neuritis due to non-vascular causes in many cases is bilateral and is associated with irritation of the small nerve trunks or sensory nerve endings. Neuritic pains often are decreased by heat and aspirin and are aggravated by cold.

Diseases of the Bones, Joints and Bursa: Flattening of the longitudinal and transverse arches often causes pain in the feet on walking. The pain may persist after resting fifteen to twenty minutes and is relieved by arch supporters. Back aches and leg aches may occur from flat feet and poor posture. Diseases of bursa (calcific and non-calcific) are associated in the acute stages with red, hot, swollen, tender areas adjacent to joints. In the subacute states there is local tenderness with limitation of motion.

Systemic Disease as a Cause for Pain in the Extremities: Diabetes mellitus, pernicious anemia, rheumatoid arthritis, disseminated lupus erythematosus, periarteritis nodosa, leprosy, tabes, and other diseases may produce symptoms simulating disease of the vascular system.

Infection: Infections of tissues, for example erysipelas, often simulate vascular disease. Often infections as well as vascular disease may be present which is common with diabetes.

Diseases of the Blood: Polycythemia, sickle cell anemia, pernicious anemia, leukemia, thrombocytopenic purpura and other blood diseases often simulate vascular disease.

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CHAPTER 27

Physical Examination

GENERAL EXAMINATION

A GENERAL physical examination is necessary because disease of the peripheral vessels often is associated with systemic disease states. Also many patients with peripheral vascular disease ultimately undergo surgery, which can be advised only with a knowledge of the patient's general health Special attention is paid to the skin, eyes, nose, throat, heart, abdomen, rectum, pelvis and nerves.

Skin: Abnormalities of the skin may suggest disease involving the arterial system, for example, yellow plaques about the eyes (xanthoma palpebrarum) or nodules in the corium and around the tendons (xanthoma tuberosum) suggest atherosclerosis; butterfly lesions on the nose and cheeks suggest disseminated lupus erythematosus and nodules on arteries suggest polyarteritis nodosa.

Eyes: Opthalmoscopic examination of the retina and its arteries may reveal arterial disease. Arteriosclerosis is present when tortuous irregular arteries exhibit silver wiring and nicking of veins. Diabetes is suggested when capillary aneurysms are present in the retinal or scleral blood vessels Necrotizing arteriolitis is suggested when retinal hemorrhages are present. Syphilis is suggested when gun-barrel vision or irregular pupils, which do not respond to light, are present.

Nose: A perforated nasal septum and "mulberry molars" suggest the presence of congenital syphilis, which may be associated with aneurysms of the arch of the aorta.

Heart: Examination of the heart may reveal atrial fibrillation which may explain an acute peripheral arterial obstruction because of the frequent association of left atrial thrombosis with

peripheral emboli. An abnormal electrocardiogram may suggest coronary artery disease, often associated with arteriosclerosis obliterans of the peripheral arteries. The presence of congestive heart failure that is due to coronary arteriosclerosis may be associated with arteriosclerosis obliterans.

Abdomen: An abdominal mass due to neoplasm of the pancreas or other organs may explain peripheral thrombophlebitis because of the frequent association of carcinoma and thrombosis. A pulsating abdominal mass usually is a sign of arteriosclerosis of the abdominal aorta with aneurysmal formation.

Prostate: Carcinoma of the prostate, uterus or ovaries may be present and may be associated with painful legs (due to nerve trunk involvement), peripheral edema, or thrombophlebitis.

NERVES: The neurologic examination may be abnormal and suggest syphilis, diabetes, cerebral arteriosclerosis or other diseases which often are associated with peripheral vascular disease. Neuritis due to pernicious anemia, malnutrition and leprosy may simulate vascular disease but may not be associated with disease of vessels.

PERIPHERAL VASCULAR EXAMINATION

The peripheral vascular examination is carried out by studying systematically the arteries, veins, capillaries and lymphatics. Certain non-vascular structures that may give rise to signs and symptoms resembling those produced by disease of the vascular system are studied also. The order of the examination usually is inspection, palpation and auscultation. The examination begins with inspection of the skin.

SKIN

Texture: With arterial disease the skin of the extremities may be thin and atrophic The skin may be wrinkled and loose if the part has been elevated (figure 293A) or it may be smooth and tense if the part has been dependent (figure 293B). Areas of ecchymosis (hemorrhage under the skin) that cannot be blanched by manual compression of the ecchymotic area may be present (figure 294A). In contrast, local discolorations due to distention of vessels blanch with pressure (figure 294B). The skin may be

thickened with chronic lymphedema or it may be hard and board-like with scleroderma. Eczematoid lesions due to stasis may be present on the lower extremities in patients with chronic venous insufficiency or venous obstruction (figure 295). Epidermophytosis may be observed as cracks between the toes.

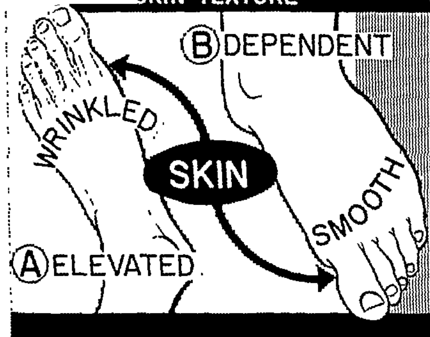


Figure 293. In the presence of arterial disease the skin may be wrinkled when the limb is elevated (A) or be swollen and tense when the foot is dependent (B)

Spider Telangiectasia (figure 296): These are also called spider nevi and spider hemangiomas and are vascular lesions located in the skin (A) consisting of red central points (heads) from which branches (legs) extend peripherally (B). Blood flows from the central point to the periphery. Blanching the spider by applying pressure to the head with a dull pointed instrument, such as a blunt pencil (C), and observing the way the blood drains out

demonstrates this. Also the central point is elevated and pulsations may be seen if the lesion is compressed with a glass slide (D). The lesion is often warmer than the adjacent tissues. Spiders usually are found on the head, neck, chest, arms and hands and are less common on the legs and feet (A). They may be found in normal subjects, during pregnancy, and in patients with parenchymatous disease of the liver but are not common in patients with obstructive jaundice in the early stages.

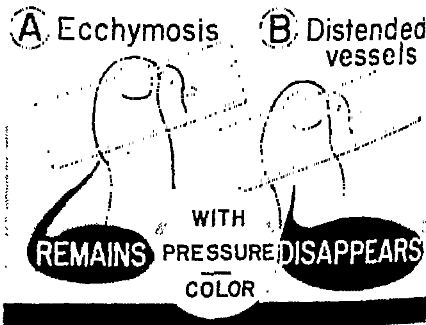


Figure 294 When an ecchymosis is present the discoloration will remain even after pressure by a glass slide (A). When discoloration is due to distended blood vessels the color will disappear with pressure by a glass slide (B).

Venous Stars (figure 297): These are also called dilated cutaneous venules and are vascular lesions which are tributaries of larger veins. They are found in all age groups and are more common in females than in males. Blood flows from the smaller vascular branches centrally to the larger collecting veins (A, B). The lesion is purple, red or blue. The lesions are usually located on the trunk, below the ribs and on the lower extremities, but

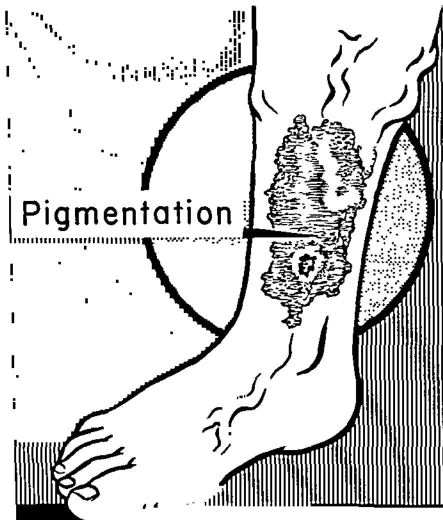


Figure 295. Stasis dermatitis from venous disease is common on the inner aspect of the ankle above the malleolus

rarely on the head and neck (C). The lesions are associated with deep vein thrombosis and venous insufficiency, or are often present in normal subjects without apparent cause.

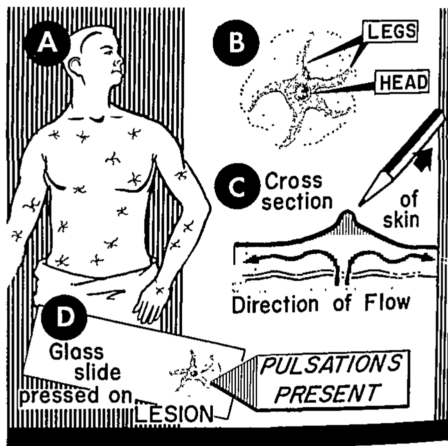


Figure 296. Spider telangiectasia occur commonly in the skin especially over the trunk, abdomen and arms and may be found in normal individuals and in those with liver disease

Capillary Angioma (figure 298): These are often called cherry or senile angiomas as they are common in elderly patients, however they are seen also during youth and middle age. The lesions are bright red, domelike and about 0.5 mm in diameter (B).

VENOUS STARS

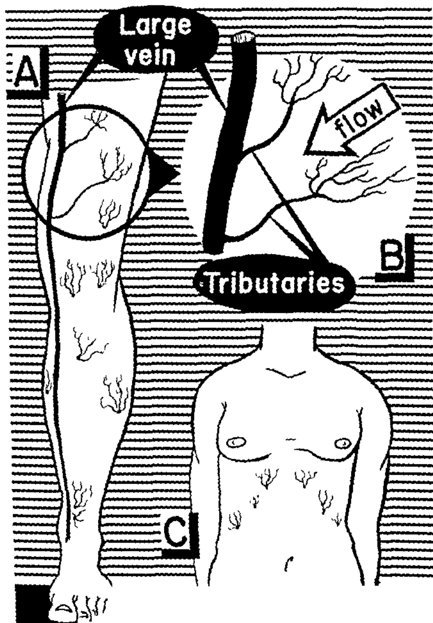


Figure 297. Venous stars are dilated venules which may occur normally or in patients with venous obstruction or insufficiency.

They are located on the abdomen and limbs but are rare on the head and neck (A). After release of compression, the lesion fills slowly with blood. It does not pulsate.

Ulcers (figure 299): An ulcer is an open sore (disruption of an *epithelial surface attended often by suppuration) which may be* hot or cold. Hot ulcers are commonly due to infections, gout and

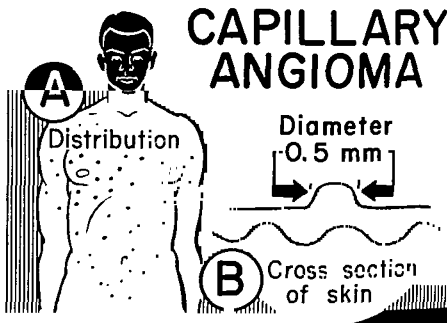


Figure 298. Capillary angiomas are small blood vessel tumors which have no clinical significance.

AV fistulas and may be located almost anywhere on the body (A). Cold ulcers often are due to ischemia associated with arterial disease, including arteriosclerosis obliterans, thromboangiitis obliterans, etc (B). Ischemic ulcers of arteriosclerosis obliterans occur characteristically over the pressure areas, such as on the tips of the toes, the metatarsal heads, dorsum of the foot and on the heels. These ulcers are often punched out with a gray sloughing base and suppurative discharge. Ulcers may be present in

areas where epidermophytosis has lowered the skin resistance, i.e., between the toes where sinus tracts or abscesses may develop.

Gangrene: This is a sign of arterial disease and may be dry or wet.

Dry (figure 300A): This is a mummifying of tissues caused by inadequate arterial circulation Dry gangrene occurs with the

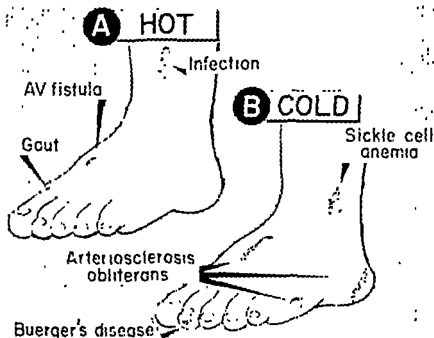


Figure 299 Hot ulcers include ulcers due to infection, A-V fistulas and gout (A) while cold ulcers include those due to sickle cell anemia, arteriosclerosis obliterans and Buerger's disease (B)

arterial occlusive diseases, such as arterial embolus or thromboses, or arteriosclerosis. Often in Raynaud's disease the gangrenous areas are 1 mm or so in diameter, appearing as small pits on the tips of the fingers. The nail is curved, the finger tip shortened, often pointed, and the soft tissues pull away from the under sur-

face of the nail. With scleroderma the gangrene usually involves one or more digits and is associated with board-like, nondistensible skin. With a large arterial embolus gangrene involves an entire limb. With arteriosclerosis the gangrene may involve large or small parts depending upon the artery involved. Adjacent to

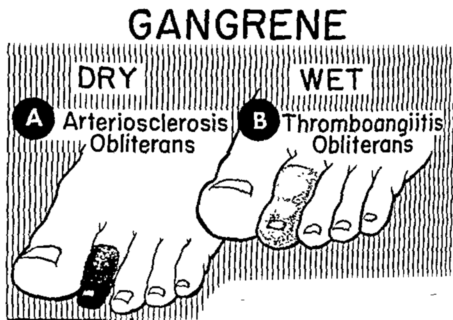


Figure 300. Dry gangrene consists of mummification of the tissues due to lack of blood supply (A) while wet gangrene is due to infection or venous obstruction (B).

areas of dry gangrene there may be swelling where the tissue resistance to infection is low.

Wet (figure 300B): Wet gangrene is seen when infection occurs or when congestion of the part is present. It is found commonly in patients with diabetes or with thromboangiitis obliterans, when venous obstruction occurs with disease of the artery.

Scars (figure 301): These appear spontaneously on the legs and are associated with arterial insufficiency and with obstructions to small arteries. The scars represent areas of atrophy of the tissues,

in which pigmentation is common. Scars may occur also in some patients as a result of minor trauma.

Infection (figure 302): This is common around the nails (paronychia) where it may have been initiated by trauma, by hangnails or by cutting the nails too short. Infections such as

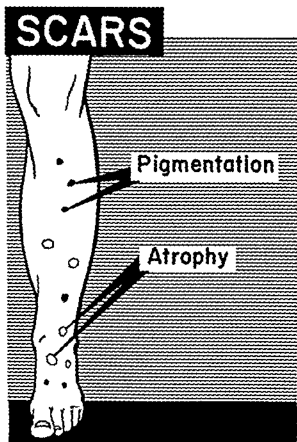


Figure 301 Localized pigmentation and atrophy of the tissues often follow small artery obstruction.

cellulitis often complicate diseases of the vascular system, such as idiopathic lymphedema, in which recurrent infections are common (B).

Nodules (figure 303): These may be visible on inspection or may be detected only by palpation. Vascular nodules (A) may

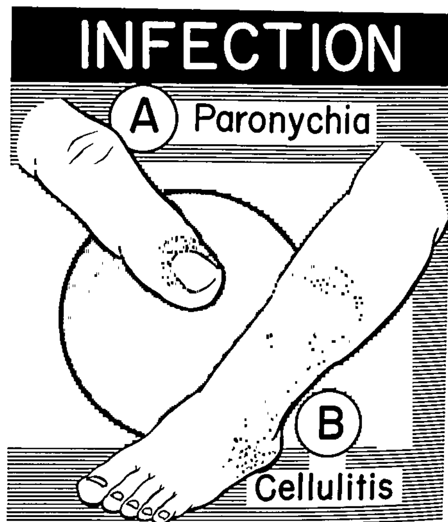


Figure 302 Paronychia is often secondary to vascular disease in the hand (A) while cellulitis commonly complicates arterial, venous or lymphatic disease in the leg (B).

involve arteries, i.e., polyarteritis nodosa, while non-vascular nodules (B) occur with fat tumors (lipomas), nerve tumors (neuromata), etc.

Atrophy: This appears as thin shiny wrinkled skin and is common in patients with arterial insufficiency. Loss of hair on the

toes often accompanies skin atrophy. In normal subjects hair on the toes is present.

Hypertrophy: This occurs with chronic lymphedema and may be secondary to venous obstruction or venous insufficiency. Chronic stasis dermatitis of the inner aspects of the lower third of the leg is associated with these conditions.

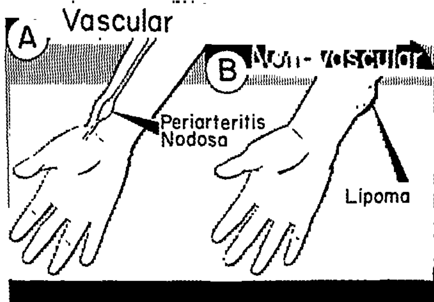


Figure 303 Vascular nodules appear in patients with periarteritis nodosa (A) while non vascular nodules are common in patients with lipomata (B).

Turgor (figure 304): The skin turgor is tested by pinching up a portion of the skin and letting it snap back. If it returns quickly the turgor is normal. If it returns slowly there is loss of turgor, which is abnormal. Skin turgor is poor with advanced arterial disease, dehydration, and degeneration of the tissues from any cause.

Temperature: For the clinical estimation of skin temperature it is desirable to have the patient's limbs exposed to the atmosphere

in a draftless room for 10 minutes or more before observations are made. The temperature of the skin depends upon the amount of heat delivered to it by the blood and the amount of heat lost from it by evaporation, conduction and convection. Normally the skin temperature should be similar on both sides of the body. A dif-

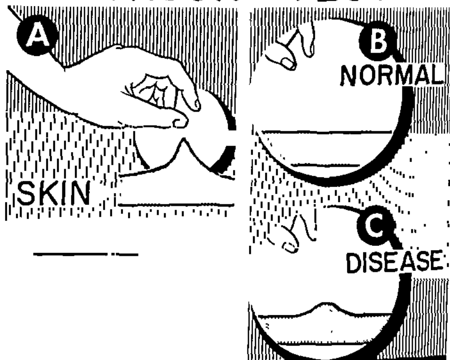


Figure 301 Normal skin turgor is present when the skin is lifted and on release it snaps back quickly (A and B). In various disease states on release the skin returns slowly to its previous state (C).

ference in temperatures of 1 or 2 degrees C of the toes of the two feet or the fingers of the two hands is abnormal. With individuals in a comfortable warm environment, the following temperature relationships are common: 1) In normal subjects usually the hands are warmer than the feet. 2) With hypothyroidism the

hands and feet are both cool. 3) With hyperthyroidism the hands and feet are both warm. 4) Normally the thumb is warmer than the little finger and the large toe is warmer than the small one (figure 242). Temperature differences due to disease are most apparent after a vasodilating procedure, such as a warm environment, or after a vasodilating drug. 5) Normally there is a negative temperature gradient from umbilicus to wrist and from umbilicus to ankles. The gradient from ankle to toes and wrists to fingers is variable and depends upon the amount of vasomotor tone present (figures 243, 244). The temperature of the toes is usually lower with the patient in the standing or sitting position than in the supine position because of postural reflexes that cause vasoconstriction in the toes. Localized hot areas on the skin suggest infection, in which case there is also rubor, tumor and dolor. Hot areas are also found in patients with arteriovenous fistulas. The temperature is related to the volume flow of blood through the part. A cool limb is in general associated with a low flow and a warm limb with a larger flow

Color: The color of the skin gives important information about the peripheral circulation The intensity of color is determined in part by the state of capillary vasodilatation or constriction. When the cutaneous capillaries are constricted the color is light; when they are dilated the color is dark The color (pink, blue or red) depends upon the amount of oxygen saturation of the blood, which in turn is related to the velocity of the blood flow through the capillaries. When the velocity is slow the oxygen saturation is low and the color is blue These relationships are illustrated in figure 305.

Relationship of Color and Temperature to Peripheral Circulation (figure 305): The important color temperature combinations are as follows: 1) cool, pale and pink, 2) cool and deep blue· 3) cool and deep red, 4) warm and pale pink, 5) warm and deep blue, and 6) warm and deep red. We may recall from the section on hemodynamics that the following relationships exist: 1) doubling the cross sectional area of a vessel halves the velocity when the volume flow is constant; 2) doubling the diameter of the vessel reduces the velocity to one-quarter of the previous level; 3) if the diameter of the vessel is doubled the resistance

decreases to $^1/_{16}$ of its former value and the blood flow is increased sixteen times; 4) if the area of the vessel is doubled the resistance is decreased to one-fourth of its previous value and the flow is increased four times.

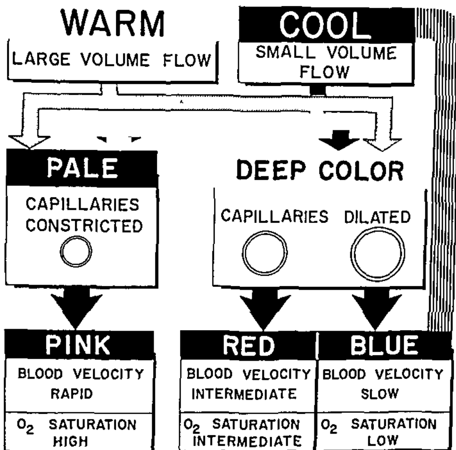


Figure 305 Relationship of color and temperature of the skin to circulatory hemodynamics

Cool and Pale Pink (figure 305): The limb is cool because the volume flow is small. It is pale because the capillaries are constricted and pink because the velocity is rapid and the oxygen saturation is high. This type of limb is seen in patients with arteriosclerosis obliterans, especially when the limb is elevated.

It may occur also with functional vasoconstriction in normal individuals.

Cool and Deep Blue (figure 305): The part is cool because the volume flow is small. It is deeply colored because the capillaries are dilated and it is blue because the velocity flow is slow with a resultant low oxygen saturation. This may occur with arterial or with venous disease. With arterial disease, arteriolar constriction lowers the head of pressure distal to the constricted site. For this reason velocity becomes slow. Also the velocity is slow because the capillary becomes atonic and dilates.

Cool and Deep Red (figure 305): The part is cool because the volume flow is small. The color is deep because of the cutaneous capillary dilatation and it is red because the blood flow is sufficiently rapid to prevent undue oxygen saturation. This color is seen often in patients with arterial disease after the foot has been elevated and then depressed. While the foot is in the elevated position the vessels are ischemic and vasodilating metabolites are liberated. When the foot is in the dependent position blood flows rapidly but in small quantities through the somewhat dilated vessels.

Warm and Pale Pink (figure 305): The part is warm because the volume flow is large. It is pale because the cutaneous capillaries are constricted and it is pink because the velocity of flow is rapid with high oxygen saturation of the blood. These are the normal color temperature relationships.

Warm and Deep Blue (figure 305): The skin temperature is warm because the flow is large. The color is deep because of dilated cutaneous vessels. The part is blue because the velocity is slow with resultant oxygen desaturation. This state of affairs is often found with venous obstruction in which the venous circulation in the limb is impaired Arterial occlusive disease characteristically does not produce these signs.

Warm and Deep Red (figure 305): The skin is warm because the volume flow is large, the color is deep because the cutaneous vessels are dilated and it is red because the velocity flow is sufficiently rapid to prevent undue oxygen desaturation. This type of reaction is found in normal subjects with inflammation of the skin.

Edema of the limbs may or may not be related to vascular disease. Some of the common causes are as follows:

Venous Insufficiency or Venous Obstruction: There is a pitting edema below the site of the insufficiency or obstruction. It is aggravated by dependency and improved by elevation of the limb. It is associated with a feeling of heaviness or congestion when swelling is present.

Congestive Heart Failure. The edema is associated with signs of right, and often left, ventricular congestive heart failure. The edema is pitting and is associated with a high venous pressure in the upper and lower extremities.

Malnutrition. This produces a pitting edema which is generalized and is associated with a low plasma protein and with a history of inadequate food intake.

Nephrosis or Nephritis: The edema is pitting and is prominent around the eyes where tissue pressure is low, as well as in the limbs. Albuminuria, low plasma protein and signs of kidney disease are present.

Cyclic Edema. This is associated with water retention which occurs in some females during or prior to the menstrual cycle.

Lipedema: This is a condition associated with obesity of the legs and hips. There is unusual sensitivity of the skin to pressure.

Mechanical Edema (Physiologic Edema): This occurs in normal subjects as a result of the foot-down position for long periods of time, e.g., when riding in a vehicle on a trip lasting several hours.

Aldosteronism: Excessive secretion of aldosterone produces sodium and water retention and edema.

Callouses: These occur at pressure points, such as over the metatarsal heads. Callouses may initiate the formation of abscesses or sinus formation when arterial insufficiency is present.

Hair (figure 306): The hair on the toes may be diminished or absent with arterial disease, e.g., with diabetes.

Nails (figure 307): Often there is thickening of the nails with or without superimposed epidermophytosis. In diabetic patients the nails are yellow.

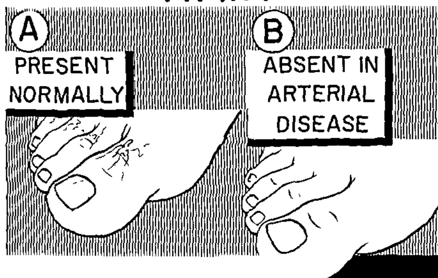


Figure 306. Hair is present on the toes normally (A), however it is absent in certain patients with arterial disease (B)

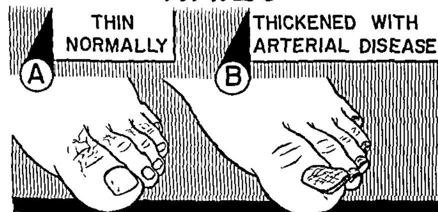


Figure 307. Normally the toenails are thin (A). With arterial disease the toenails may be thickened and deformed (B).

Thrills and Murmurs: Thrills are common over arteriovenous fistulas. Murmurs are heard characteristically over the abdominal aorta if arteriosclerosis or an aneurysm is present. The murmurs may be heard over the iliac and femoral arteries when partial occulsion of these vessels occurs.

Tenderness: This is characteristic of vascular and non-vascular abnormalities. It may be present with arterial obstruction, ischemic tissues, acute superficial or deep thrombophlebitis, acute lymphangiitis and diseases of the capillaries that produce capillary leakage (angioneurotic edema or capillary fragility). Abnormalities of bone (tumor), muscle (dermatomyositis), nerves (nutritional neuritis) and other nonvascular structures are also causes of tenderness.

THE UPPER EXTREMITIES

The upper and lower extremities are examined separately employing different techniques keeping in mind the various vascular diseases which affect these extremities.

Diseases of: *The arterial diseases which affect the upper extremities* commonly are Raynaud's disease, thromboangiitis obliterans, scleroderma and abnormalities of the shoulder girdle.

Raynaud's Disease. This is characterized typically by normal palpable pulsations of the axillary, brachial, radial and ulnar arteries with evidence of disease of the digital arteries (1). Inspection reveals atrophy of the tips of the fingers often with small, one millimeter pits at the tips which represent infarcts (figure 361) Absorption of bone of the terminal phalanges may occur (figure 208) with atrophy of the tissues resulting in pointing of the finger tips and a retraction of soft tissue of the pad away from the fingernail. The fingernail may be abnormally curved and ridged. (See chapter on Raynaud's.)

Thromboangiitis Obliterans: This is characterized by absence of ulnar artery pulsations with disease of the digital or medium sized arteries, nerves and veins. The ulnar artery is best felt with the patient in the supine position with the arm 45 degrees from the body and the hand dorsiflexed (figure 308). In this position the artery is thrown forward and palpation is facilitated (See chapter on Thromboangiitis Obliterans.)

Scleroderma: This is suggested when the skin of the hands, arms, and other portions of the body are hard and inelastic. Pigmentation, depigmentation and calcification of the skin may occur. The disease involves the trunk, legs and viscera as well as the arms and hands. (See chapter on Collagen Diseases.)

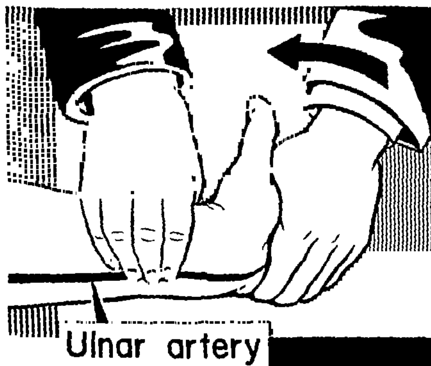


Figure 308 The ulnar artery is palpated easily with the patient in the supine position when the hand is dorsiflexed

Abnormalities of the Shoulder-girdle: These produce transient obstructions of arteries and irritation of nerves which may result in pain and atrophy of the tips of the fingers. These disorders include scalenous anticus syndrome, cervical rib, hyperabduction syndrome, costoclavicular syndrome and the malposition syndrome. These conditions have in common the production of pains in the hands or arms with movement of the head, arms or

shoulders. (See chapter on Neurovascular Syndromes of the Upper Extremities.)

Locating Arterial Obstructions: The subclavian, axillary, brachial, radial and ulnar arteries should be palpated and the force of the pulses compared bilaterally and in the upper and lower extremities. Obstructions of the following arteries produce characteristic findings:

Subclavian Artery Obstruction: This results in absent pulsations distal to the obstruction that is in the axillary, brachial, radial and ulnar arteries.

Axillary Artery Obstruction: This is revealed by absent brachial, radial and ulnar artery pulsations and the subclavian artery pulsations are normal or increased.

Brachial Artery Obstruction: This is revealed by absent pulses in the radial and ulnar arteries with normal or increased pulses in the axillary artery.

Ulnar or Radial Artery Obstructions at or Proximal to the Wrist: These are revealed by absent pulsations of either of these arteries at the wrist with palpable pulsations of the brachial artery.

Ulnar, Radial or Metacarpal Artery Obstructions Distal to the Wrist: These may be identified with the Allen Test (3).

ALLEN TEST: The test is carried out as follows (figure 309): The hands of the patient are held in front of him as he faces the examiner. If obstruction of an ulnar artery is suspected the examiner compresses the radial artery and the patient clenches his hand repeatedly while compression of the radial artery is maintained by the examiner. If the arterial tree is intact the normal pink color decreases slightly and is replaced within a second or two by normal color If the ulnar artery is occluded by disease pallor occurs and is maintained as long as the radial artery is compressed. *When compression is released reactive hyperemia develops.* Repetition of the test with the examiner compressing the ulnar artery demonstrates the presence or absence of a lesion in the radial artery

THE FREEMAN MODIFICATION OF ALLEN TEST IS AS FOLLOWS (figure 310): The patient sits in a chair. The arm is elevated and the brachial artery is occluded manually. Active exercise of the hand is carried out (A). *The hand is then placed on the lap*

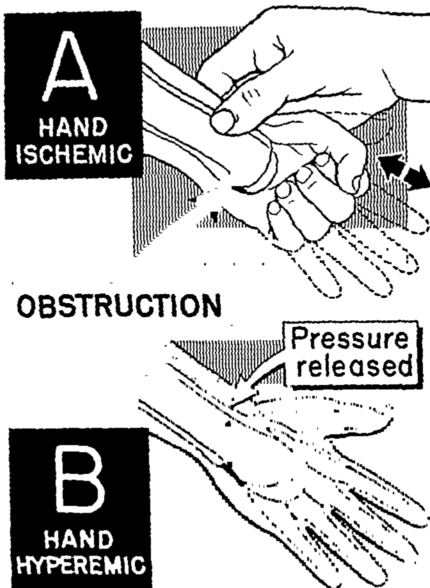


Figure 309. The Allen test mav be employed to detect obstructions in the ulnar artery distal to its point of palpability at the wrist The physician manually compresses the radial artery. The hand is exercised and if obstruction is present, the hand becomes ischemic (A) The manual compression is released and the hand becomes hyperemic (B).

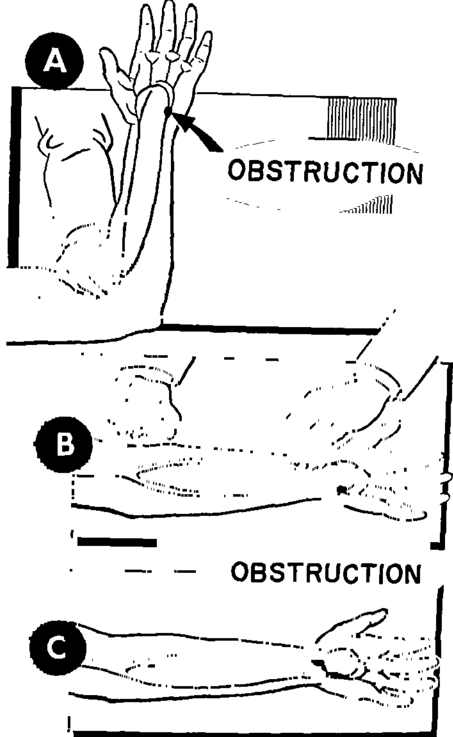


Figure 310. A modification of the Allen test is as follows: The brachial *artery is compressed manually and the hand is exercised (A).* The radial artery is next compressed after which the brachial artery is released (B). If an obstruction is present in the ulnar artery the hand will be ischemic. The radial artery is then released and the hand becomes hyperemic (C).

where the palm can be observed. The radial artery is occluded manually after which the brachial artery is released (B). With obstruction of the ulnar artery the hand remains ischemic as long as pressure is applied. On release of radial compression (C) the hand becomes hypermic (4). The test may be repeated obstructing the ulnar artery which gives information relative to the patency of the radial.

Locating Obstructions in the Dorsalis Pedis and Posterior Tibial Arteries Proximal and Distal to the Ankle: This may be carried out using similar techniques (vide supra).

Tests for Vascular Abnormalities of the Shoulder Girdle: These states include anterior scalenus, cervical rib, costoclavicular and the hyperabduction syndrome.

Sclaneus Anticus Maneuver (Adson) (figure 367): The patient sits with the forearms on his knees and the examiner feels the radial pulse. The head is extended, the chin is elevated and he looks toward the arm being palpated and his breath is held in inspiration (5). A positive test occurs when the wrist pulse is diminished or obliterated and pain is produced in the ipsilateral arm The test should be repeated with the patient looking straight ahead with breath holding to be sure that breath holding alone is not responsible for the diminished pulse.

Cervical Rib Maneuver: A cervical rib may produce spasm or swelling of the scalenus muscles in which case the scalenus anticus maneuver (vide supra) will be positive

Costoclavicular Maneuver (figure 369): The patient sits, the shoulders are pulled back and downward. If pinching of the neurovascular structures between the first rib and the clavicle occurs, the pulse is obliterated or diminished on the involved side and there is pain in the arm (6). The pain is relieved and the pulse returns by pulling the shoulders up and forward.

Hyperabduction Maneuver (figure 370): The arm is elevated above the head and the pulse is palpated (7). Stretching of the artery around the corocoid process or compression by the pectoralis minor may produce obstruction to the artery which abolishes the pulse and produces pain in the hand. Arterial obstruction may be confirmed by having the patient open and close his hand repeatedly with the hand in the elevated position which

produces pallor due to ischemia. The hand is lowered to heart level and reactive hyperemia develops if obstruction has been present.

THE LOWER EXTREMITIES

The important aspects of the physical examination of the lower extremities are: 1) palpation, 2) elevation and dependency tests, and 3) venous filling tests.

Palpation of Arteries: The pulsations of the arteries of the lower extremities should be palpated and compared with the pulsations of similar arteries of the upper extremities. This is important in locating obstructions in the arterial tree (2, 8). For example, a low cardiac output reduces the pulsations to the upper and lower limbs while peripheral vascular disease reduces the pulses locally. Likewise a high cardiac output increases the pulsations to the arteries of the upper and lower extremities while an inflammatory lesion in one limb increases the pulsations locally. If there is a question of low cardiac output blood pressure measurement and auscultation of the heart may reveal low pressure and diminished heart tones which suggest that this condition exists. The following arteries should be palpated:

Abdominal Aorta: This should be palpated in all patients to diagnose aortic aneurysms. An expansile pulsation at or below the navel is suggestive of this condition (figure 311). One hand is placed on the abdomen on each side of the vessel and, in the presence of an aneurysm, a pulsation is felt which forces the fingers apart with each cardiac systole.

Iliac Arteries· Aneurysms of the iliac arteries may be palpated below the navel in the right or left lower quadrant.

Common Femoral Artery (figure 312): This artery may be palpated distal to Poupart's ligament midway between the anterior spine of the ilium and the symphysis pubis. The structures which are present in this region naming them from the iliac crest toward the symphysis pubis are indicated by the mnemonic word "NAVEL" (*N*erve, *A*rtery, *V*ein, *E*mpty space and *L*ymph nodes).

The Superficial Femoral Artery: The pulsations in the thigh may be felt above or in the region of Hunter's canal in a few thin

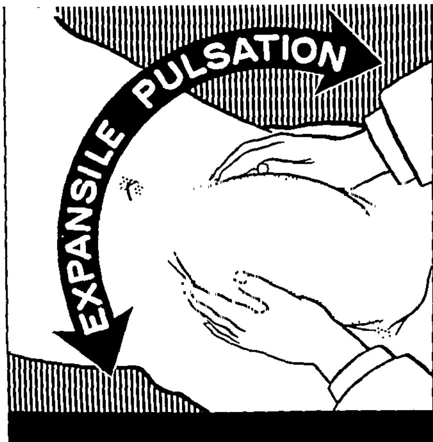


Figure 311. An expansile pulsation is present in the abdominal region when an abdominal aneurysm is present

individuals. Palpation of this region is important as arteriosclerotic lesions often are located here.

Popliteal Artery (figure 313): The pulsations of this artery normally are difficult to feel especially in obese individuals. The vessel lies in the midline of the popliteal space behind the knee.

It may be felt with the patient supine, with the knee flexed with the foot on the bed. Also it may be felt with the patient in the sitting position with the examiners fingers in the popliteal space and the thumbs on the knee-cap.

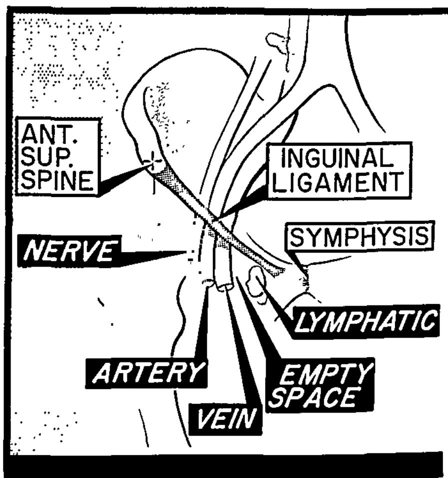


Figure 312. Relationship of the femoral artery to other structures in the groin

Dorsalis Pedis Artery (figure 314): This is a continuation of the anterior tibial artery and is found on the dorsum of the foot by drawing a line from the center of the space between the two malleoli to the proximal medial portion of the first metatarsal

bone. Morrison found that normally the dorsalis pedis artery pulsation was absent in 19 per cent of 1000 cases studied (9).

Posterior Tibial Artery (figure 315): This artery is felt at a point two-thirds the distance from the heel to the posterior aspect of the internal malleolus. In palpating the patient's right posterior tibial artery the physician stands on the patient's right and reaches

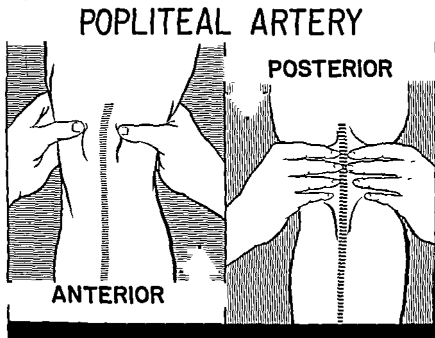


Figure 313 Technique of palpating popliteal artery.

over the internal malleolus and palpates the artery with the fingers

Differentiation of the Patient's Pulse from Examiner's Pulse: At times it is difficult to differentiate pulsations which originate from the patient from those which originate in the examiner's fingers. Separate counting of the physician's and patient's pulse rate is helpful. The magnitude and frequency of the patient's pulsations may be increased by giving $^1/_{100}$ grain nitroglycerin (10) or by exercise.

Intensity of Pulsations: It is advisable to list the intensity of

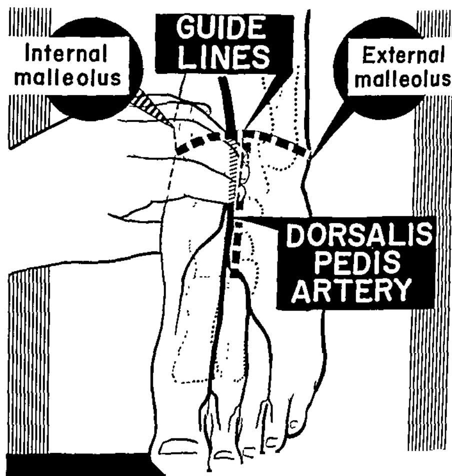


Figure 314. Technique of palpating dorsalis pedis artery.

Figure 315. Technique of palpating posterior tibial artery

the pulsations according to a chart. The intensity of the pulses may be from one to four plus.

Elevation and Dependency Test (figure 316): This is a good test for determining the presence or absence of arterial disease (11, 12). The patient lies on his back with the legs elevated to an angle of 90 degrees and he flexes and extends his feet repeatedly for one minute (A). With impaired arterial flow a waxy white

color develops. He then assumes the sitting position (B). With arterial disease the foot becomes a bright red (reactive hyperemia). With mild arterial disease pallor develops late after elevation and reactive hyperemia develops in from fifteen to twenty seconds. With moderate arterial disease the pallor occurs earlier and the reactive hyperemia develops in from forty-five to sixty seconds. With advanced disease the test may not be positive as

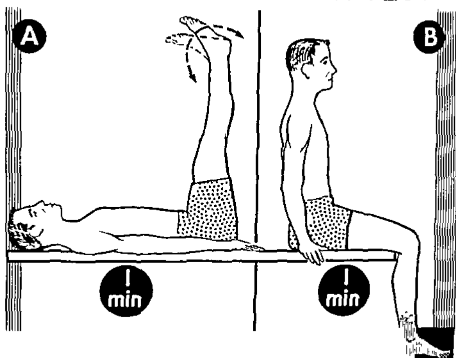


Figure 316. Reactive hyperemia test produced by elevation (A) and dependency (B).

maximal reactive hyperemia is present even before the legs are elevated.

The mechanism of the test is as follows: Elevation of the legs produces ischemia which releases vasodilating substances. The dependent foot position allows gravity and the force of the cardiac contraction to deliver blood to the dilated vessels in the feet.

Blood Pressure in Skin Vessels: Gilfillan, Freeman and Leeds (13) have described a method for the measurement of the blood pressure in the minute vessels of the human skin to be used in differentiating functional from organic disease and in selecting proper treatment for patients with vascular diseases. The test consists of raising the foot 65 cm above the auricle (phlebostatic level) for two minutes and then applying occlusive cuffs for five minutes. If within one minute after release of the cuffs reactive hyperemia does not appear, the feet are gradually lowered until flushing takes place and the height of this level is noted. Ten normal controls were seen to flush at the standard height of 65 cm above the table in from fifteen to forty-five seconds. In the diseased subjects the heights varied The lower limit of pressures necessary to allow spontaneous healing of necrotic lesions under the conditions described seemed to be in the magnitude of 35 cm above the phlebostatic level. A similar limit for successful performance of amputation at the level of the forefoot or toes seems to exist at about 45 cm above the phlebostatic level.

Venous Filling Test: This test may be carried out at the same time as the elevation-dependency test as the techniques for performing the test are similar. The legs are elevated for one minute after which the patient assumes the sitting position. The time required for the veins to fill is measured (14). Arterial obstruction is suspected when the onset of filling is greater than thirty seconds. When venous filling time is short, venous insufficiency is suspected. Afte [illegible]
femoral artery, [illegible]
seconds. The degree of filling of the veins is determined best by estimating the amount of distention of the veins by palpation. When the veins are partially filled often no significant differences in the size of two different veins can be observed, however, differences in pressure within the veins can be palpated It should be recalled that Laplace's law states that the tension on the wall of a tube is greater when the diameter of the tube is large so that large veins will feel more tense than small ones merely because of the difference in diameter. This should be kept in mind when palpating veins.

Exercise Venous Filling Test: A satisfactory test employed in our laboratory for demonstrating arterial insufficiency is as follows: The patient stands for thirty seconds in a warm environment to encourage venous filling. He then trots rapidly in place for fifteen seconds after which he again stands. If arterial disease is present the veins collapse quickly during exercise and fill slowly at rest. Normally the veins decrease in size slightly with exercise and fill rapidly (usually within fifteen seconds). Arterial disease is present if the venous filling is prolonged (15). This test is reliable only if venous disease is absent.

THE PRESUMPTIVE DIAGNOSIS

Following the physical examination a presumptive diagnosis should be made. The diagnosis should include an etiologic, anatomic, physiologic and functional diagnosis.

The Etiologic Diagnosis: This includes arteriosclerosis, syphilis, thromboangitis obliterans, tuberculosis, etc.

The Anatomic Diagnosis: This describes the vessel or vessels or anatomic defects which are present, for example aortic aneurysm or occlusion of a right or left popliteal artery.

The Physiologic Diagnosis: This describes the functional disturbance which is present for example ischemic pain after walking.

Functional Diagnosis: This is graded on the basis of I to IV. Grade I indicates a patient who suffers no limitation from his disease. This would be characteristic of a patient who has had thrombophlebitis involving a small segment of a superficial vein. Grade II indicates a patient whose activity is limited slightly. For example, a patient with arteriosclerosis obliterans who can walk at least four blocks without claudication. Grade III indicates an ambulatory patient with severe symptoms, i.e., he can walk less than 1/2 block. Grade IV indicates a bedridden patient.

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Slowed blood stream
Exposure to radiation
Idiopathic
Leriche syndrome

6. EMBOLISM
   - Blood
   - Fat
   - Air
7. COLD INJURIES
   - Chilblains (Pernio)
   - Frost bite
   - Trench foot
   - Immersion foot
8. AINHUM

II. NON-OCCLUSIVE

1. ANEURYSMS
   - Congenital
   - Acquired
2. ARTERIOVENOUS FISTULAS
   - Congenital
   - Acquired

FUNCTIONAL

I. VASOCONSTRICTOR

1. RAYNAUD'S DISEASE
   - Primary
   - Secondary
2. ACROCYANOSIS
3. LIVEDO RETICULARIS
   - Marmorata
   - Idiopathica
   - Symptomatica
4. ERGOTISM
5. SHOULDER GIRDLE SYNDROMES
   - Scalenous anticus
   - Cervical rib
   - Costoclavicular
   - Hyperabduction
   - Thoracic outlet
   - Malposition
   - Pectoralis minor

CHAPTER 28

Classification of Peripheral Vascular Disease

ARTERIES

ORGANIC

I. OCCLUSIVE

1. ARTERIOSCLEROSIS
    - Atherosclerosis
    - Atherosclerosis obliterans
    - Medial arteriosclerosis
    - Arteriolosclerosis and hypertensive ischemic ulceration
2. THROMBOANGIITIS OBLITERANS
3. ARTERITIS (INFLAMMATORY DISEASES)
    - Temporal arteritis
    - Nodular panniculitis
    - *Disseminated arteritis*
    - Nodular vasculitis
    - Erythema induratum
    - Erythema nodosum
    - Infectious arteritis
    - Allergic angiitis
    - Non-specific arteritis
    - Pulseless disease
4. COLLAGEN DISEASES
    - Disseminated lupus erythematosus
    - Periarteritis nodosa
    - Scleroderma
    - Dermatomyositis
5. ARTERIAL THROMBOSIS
    - *Infectious diseases*
    - Blood dyscrasias
    - Trauma or compression
    - Surgery
    - Parturition
    - Cardiac insufficiency

Infections
- Septicemia
- Systemic lupus erythematosus
- Subacute bacterial endocarditis

Splenomegaly
- Hodgkin's disease
- Leukemia
- Malignant lymphoma
- Gaucher's disease
- Banti's syndrome
- Felty's syndrome

Malignancy

Drugs and Chemical Agents
- Quinine
- Quinidine
- Ergot
- Bismuth
- *Sulfa drugs*
- Hair dyes
- Chloramphenicol
- Streptomycin
- Iodine
- Trimethadione
- Dichloro-diphenyl-trichloro-ethane (DDT)
- Digitoxin
- Arsenic
- Ally-isopropyl-acetyl-carbamide (Sedormid)
- Gold
- Phenol
- Benzine
- Dinitrophenol
- Snake venom
- Pertussis vaccine
- Certain foods, such as orris root
- Nitrogen mustard
- Triethyline melamine
- Methylphenylethyl hydantoin (Mesantoin)

Physical Factors
- Heat Stroke
- Radiation
- Burns

6. Post-Traumatic Syndromes
   - Major causalgia
   - Minor causalgia
   - Sudek's atrophy

II. VASODILATOR
   1. Erythermalgia

VEINS

ORGANIC

I. OCCLUSIVE
   1. Thrombophlebitis
   2. Thrombophlebitis migrans
   3. Phlebothrombosis
   4. Postphlebitic syndrome

II. NON-OCCLUSIVE
   1. Phlebosclerosis
   2. Phlebofibrosis
   3. Rupture
   4. Phlebectasia

FUNCTIONAL

I. PHLEBOSPASM

CAPILLARIES

I. INCREASED FRAGILITY (PURPURA)
   1. Thrombocytopenic Purpura
      - Primary: Idiopathic (Werlhoff's) disease
      - Secondary
        - Vascular Defects
          - Thrombotic thrombocytopenic purpura
          - Blood dyscrasias
            - Hodgkin's disease
            - Acquired hemolytic anemia
            - Aplastic anemia
            - Pernicious anemia
            - Leukemia
            - Myeloma
            - Malignant lymphoma

- Infections
  - Septicemia
  - Systemic lupus erythematosus
  - Subacute bacterial endocarditis
- Splenomegaly
  - Hodgkin's disease
  - Leukemia
  - Malignant lymphoma
  - Gaucher's disease
  - Banti's syndrome
  - Felty's syndrome
- Malignancy
- Drugs and Chemical Agents
  - Quinine
  - Quinidine
  - Ergot
  - Bismuth
  - Sulfa drugs
  - Hair dyes
  - Chloramphenicol
  - Streptomycin
  - Iodine
  - Trimethadione
  - Dichloro-diphenyl-trichloro-ethane (DDT)
  - Digitoxin
  - Arsenic
  - Ally-isopropyl-acetyl-carbamide (Sedormid)
  - Gold
  - Phenol
  - Benzine
  - Dinitrophenol
  - Snake venom
  - Pertussis vaccine
  - Certain foods, such as orris root
  - Nitrogen mustard
  - Triethyline melamine
  - Methylphenylethyl hydantoin (Mesantoin)
- Physical Factors
  - Heat Stroke
  - Radiation
  - Burns

2. Non-Thrombocytopenic Purpura
   - Primary
     - Senile
     - Purpura simplex
     - Hereditary hemorrhagic diathesis
   - Secondary
     - Stasis
     - Traumatic or mechanical
     - *Allergic or anaphylactoid*
       - Schoenlein-Henoch purpura
       - Purpura fulminans
     - Skin diseases
     - Chemical agents
       - Quinine
       - Chloral hydrate
       - Salicylic acid
       - *Acetophenetidin (Phenacetin)*
       - Belladonna
       - Atropine
       - Penicillin
       - Iodine
       - Bismuth
       - Mercury
     - Systemic diseases and infections
       - *Nephritis*
       - Purpura fulminans
       - Septicemia
       - Enanthema
       - Scarlet fever
     - Avitaminosis
       - Scurvy
       - Vitamin P deficiency
     - Cryoglobulinemia

II. INCREASED CAPILLARY PERMEABILITY

1. Angioneurotic Edema
2. Serum Sickness
3. Allergic Urticaria
4. Physical Irritants
   - Trauma
   - Cold
   - Heat
5. Inflammation

LYMPHATICS

I. LYMPHEDEMA

1. PRIMARY (IDIOPATHIC)
    - Congenital and hereditary (Milroy's disease)
    - Congenital but not hereditary
        - Without constricting bands
        - With constricting bands
    - Praecox
2. SECONDARY
    - Lymphangitis and lymphadenitis
        - Infection and infestations
            - Filariasis
            - Pyogenic
            - Fungus
            - Erysipelas
        - Mechanical, chemical and physical
            - Abrasions
            - Lacerations
            - Chemical irritation
            - Burns
            - X-ray
            - Trauma
        - Granulomata
            - Tuberculosis
            - Lymphogranuloma
            - Syphilis
    - Post phlebitic
    - Surgery
        - Removal of lymph nodes
        - Removal of lymph vessels
    - Neoplastic invasion of lymph nodes
        - Lymphangioma
        - Endothelioma
        - Lymphoma
        - Lymphocytoma
        - Leukemia
        - Lymphosarcoma
        - Hodgkin's disease
        - Reticular cell sarcoma
        - Sarcoma of lymph nodes

Obstruction of thoracic duct

II. LYMPHANGITIS
- 1. Primary (Idiopathic)
- 2. Secondary
  - Infection
  - Infestation
  - Trauma

TUMORS

BLOOD VESSELS

I. BENIGN
- 1. Hemangioma
  - Cavernous
  - Capillary
  - Plexiform
  - Sclerosing
  - Sturges-Parkes Weber-Dimitri syndrome
  - Von Hippel-Lindau disease
  - Maffucci's syndrome
- 2. Glomus
- 3. Telangiectasia
  - Hereditary hemorrhagic
  - Spider
  - Senile
  - Simple

II. MALIGNANT
- 1. Hemangioendothelioma
- 2. Hemangiosarcoma
- 3. Kaposi's Sarcoma

LYMPH VESSELS

I. BENIGN
- 1. Lymphangiectasia
- 2. Lymphangioma
  - Simple
  - Cavernous
  - Cystic

II. MALIGNANT
- 1. Lymphangiosarcoma

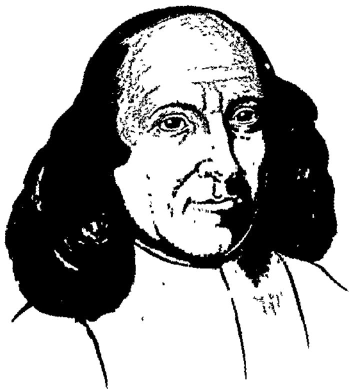


Figure 317. Marcello Malpighi 1628–1694 Founder of the knowledge of the anatomy of the tissues. In 1661, he made the important discovery of the existence of capillaries in the lungs and mesentery of the frog This discovery was the final link in the chain explaining Harvey's demonstration of the circulation, even though Harvey himself was unaware of such capillary anastomoses.

CHAPTER 29

Arteriosclerosis

GENERAL CONSIDERATIONS

ARTERIOSCLEROSIS is a generic name that applies to four forms of vascular disease. These are: 1) atherosclerosis; 2) atherosclerosis obliterans; 3) medial calcification or Monckeberg's sclerosis, and 4) arteriolosclerosis.

Arteriosclerosis may be regarded as a complex mixture of degenerative and reparative processes leading to increased rigidity, diminished elasticity and decreased caliber of arteries. Arteriosclerosis involves collagenous tissue, fibrous tissue, elastic fibers, smooth muscle and adventitia. These tissues are the usual components of arteries and each has its own requirements for survival and each reacts to injury in its own way. Blumenthal (1) has postulated that the characteristics of the arteriosclerotic lesion are determined primarily by the potential range of tissue responses of the arteries and by the nature of the exciting agent.

TISSUE RESPONSE TO INJURY

The reactive tissues are 1) the endothelium, 2) non-elastic components of the intima; 3) elastic tissue; 4) smooth muscle, and 5) vasa vasorum.

The Endothelium: This is a single layer of flattened cells lining blood vessels whose main function is to provide a smooth surface for the flowing blood stream. It serves also as a membrane through which nutrients gain entrance to underlying tissues and waste products from the tissues are discharged into the blood. It may also serve as a protective barrier against injurious agents in the circulation. The endothelial cells differ in different portions of the vascular system and they become progressively flatter with increasing age. Binucleate cells have been observed at branches.

of the aorta where the changing direction of blood flow may result in injurious mechanical effects (2). The intima is especially liable to injury because of its exposed location and the manner in which it rejuvenates after injury is significant. It is probable that cells exist in the subendothelial layer which replace the endothelium or differentiate into other vascular tissues after intimal damage (3). Damage to the endothelium results in thromboplastin formation, platelet collections, fibrin deposition and thrombosis of the vessel.

PERMEABILITY: The permeability of the endothelium is of importance in providing nutrients to the inner portion of the arterial wall (4, 5). Endothelial permeability is greater in the abdominal aorta than in the thoracic aorta or aortic arch. The permeability varies with age and with the thickness of the intima. The permeability may be increased by inflammatory reactions to such an extent that chylomicrons and certain lipoprotein particles gain entrance to the vessel wall through the endothelium (6); however these particles apparently are not able to pass into or through the normal endothelial cells. Definite intercellular gaps in the endothelial membrane have been described, which are especially apparent in inflammatory states and in circulatory disorders Winternitz (7) has demonstrated communications originating in the vasa vasorum of arteries which communicate with the lumen of the vessel. These vascular channels, however, play no role in diffusion.

SECRETING MEMBRANE. It has been suggested that the endothelium may serve as a secreting membrane (8). This suggests the possibility that intimal plaques are the result of a progressive deposition and organization of fibrin deposited on the endothelial surface.

PHAGOCYTIC FUNCTION: The endothelium may serve a phagocytic function. Lipophagia by the endothelium would be an expression of a decrease in vitality in which fatty substances may be transferred from outside into cells which can no longer repel them (3)

Non-Cellular Components of the Intima: Collagen and reticular fibers form a ground substance which is a major component of the intima and may be derived from the endothelium (3). This

substance forms a basement membrane for the endothelium and is continuous with the internal elastic membrane. Almost any kind of injury to the walls of arteries is followed by a proliferative response in the intima Even stretching of the smooth muscle components can stimulate intimal proliferation. The first response to injury is probably a deposition of sulfated mucoproteins followed by a deposition of collagenous fibers (9). This type of response is seen in the rabbit aorta made necrotic by freezing. Here the reparative process is restricted to the intima and consists of proliferation of fibroblasts followed by the formation of collagen and elastic fibers and newly formed smooth muscle cells (10).

Elastic Tissue: With human arteriosclerosis the elastic fibers increase in rigidity due to calcification or they break which results in a loss of tensile strength of the arteries (11). In addition there is reduplication and granulation of the elastic substance. With arterial injury a sulfated mucopolysaccharide containing ground substance is found in the basement membrane of the endothelium and forms a matrix for the elastic fibers Elastase, an enzyme from the pancreas which has the action of a mucase, causes these fibers to uncoil and separate (12) and represents the first stage of degeneration of the elastic layer Denatured collagen may be dissolved by elastase (13). With degeneration of the elastic fiber there is progressive deposition of calcium on the surface or within the substance of the elastic elements (2, 14, 15).

Smooth Muscle: The arterial walls have the capacity for reconstitution of smooth muscle. Occasionally an injured endothelium may be repaired with smooth muscle cells and it is probable that intimal cells may become smooth muscle at sites of injury (10). Smooth muscle cells of the media will grow into areas of injury if the elastic framework remains intact When large areas of smooth muscle are damaged repair is by scar tissue. Epinephrine and norepinephine have been shown to have a damaging effect on smooth muscle and arterial media which consists of necrosis, calcification and fibrosis Thyroxin combined with these substances is even more detrimental than epinephrine alone (16, 17).

The Vasa Vasorum: Diffusion mechanisms apparently remain adequate as long as the wall remains below a certain critical thickness As the intima thickens there develops a network

of capillaries in the thickened area which may be a compensating mechanism to nourish the tissues. These vessels may rupture, however, and initiate vascular thrombosis. Diffusion may be interfered with by high arterial pressures which compress the intima and media against the relatively inelastic adventitia and may occlude vasa vasorum and capillaries producing hemorrhage, with local cholesterol liberation and fibrous tissue formation (18).

Histologic Changes of the Aorta (Not Arteriosclerotic) Due to Age

The changes in the aorta due to age are considerably different from those due to arteriosclerosis (19) (figure 318).

Infants: The intima and subintima are fine and thin and the internal elastic membrane is a delicate, straight single structure. The media consists of muscle and collagenous fibers and the adventitia is of delicate texture.

Young Adults: The subintima increases in thickness and becomes denser. The internal elastic layer becomes thick. The media shows early replacement of smooth muscle fibers by fibrous connective tissue There is beginning disorganization of the elastic tissue and the adventitia becomes denser.

Middle Age: The subintima becomes fibrous, some areas being more fibrous than others. The internal elastic membrane splits. The elastic tissue in the media becomes disorganized. Connective tissue replaces more of the muscular media and the adventitia is thick and dense.

Senile Subjects: The intima becomes thick, fibrous and hyalinized The internal elastic membrane becomes frayed and fragmented. The media consists mostly of connective tissue and the adventitia is coarse and dense.

Etiology of Arteriosclerosis

There are essentially four major theories. These are: 1) hemodynamic; 2) lipid and metabolic; 3) filtration, and 4) inflammatory.

Hemodynamic Theory

This theory states that arteriosclerosis is the end result of local mechanical factors acting for a long period of time and is the result

NORMAL AORTA

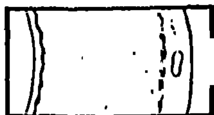








Figure 318 Changes in the aorta with age The intima is to the left.

of reparative processes to wear and tear. Some of the factors to be considered are blood pressure, tension, cardiac thrust, vibration, volume flow, gravitational forces, viscosity, friction and shearing force (20).

Blood Pressure: It has been pointed out that arteriosclerosis occurs when blood pressure is high. In the pulmonary arterial circuit arteriosclerosis occurs when pulmonary hypertension is present (21). With coarctation of the aorta arteriosclerotic changes occur proximal to the constriction but are less common distal to the obstruction. Veins which carry low pressure are relatively immune to arteriosclerotic changes. It has been postulated that high blood pressure compresses the intima and media against the inelastic adventitia and interferes with the permeability and blood flow of the vessel walls (18).

Tension: The tension on the vessel wall varies with the radius of the vessel and the difference in pressure between the inside and outside of the vessel (Laplace) (22) and there is a correlation between tension and arteriosclerosis. Tension and frequency of arteriosclerosis in the various vessels decrease in the following order: aorta, pulmonary arteries, large branching arteries, arterioles and capillaries (23). The tension of the artery wall is brought about by two main factors: 1) stretching of the elastic fibers and the recoil after stretching, and 2) vasomotor tone and pressor agents such as norepinephrine (22).

Cardiac Thrust: Ordinarily the aorta acts as a buffer which decreases the impact of the pulse waves on vessels such as the bifurcation of the aorta. As the aorta becomes more rigid the pulse waves are transmitted with greater force to the periphery thereby producing greater impact on certain vascular areas. The effect of the cardiac thrust upon the peripheral vessels becomes greater with age (20, 24).

Vibration: Vibration in the vascular system occurs with the rapid change in tension which occurs with cardiac systole and diastole. The branches of the aorta are most susceptible to this vibration (25). The natural frequency in the arteries of the arms is between 3.6 and 4.8 vibrations per second. The frequency of occurrence of atheromatous lesions in the immediate branches of the aorta including the coronary arteries suggests that these vibra-

tions may be a significant factor in the deterioration of these tissues.

Volume Flow: With each cardiac systole there is constriction of arteries and arterioles in young individuals, but this is less prominent in the aged. This constriction may occur as an adaptive phenomenon to the changes in circulating blood volume which occur with each cardiac systole. In aged individuals the rigid blood vessels cannot respond to this stimulus which may lead to degenerative vascular changes in the form of hyalinization and calcification of the smooth muscles of the arterioles. The renal vessels are particularly susceptible to this type of damage (20).

Gravitational Forces: The severity of arteriosclerosis of the abdominal aorta in many patients suggests that gravitational effects on the blood of upright patients may be of significance. Klotz (26) has pointed out that the distribution of sclerotic patches in rabbits may be changed by varying the position of the animal.

Viscosity and Friction: It is probable that considerable increase in viscosity and friction occur in the arteriolar portions of the capillaries and these factors could be important in the production of degenerative changes of small vessels.

Shearing Force: A shearing force resulting from slippage between the intima and media during contraction and dilatation of the vessel has been suggested as a cause for intimal thickening (27).

Summary of the Hemodynamic Factors: It is probable that hydrostatic tension is important in producing thickening of the arteries. In addition local lesions in the vascular system can be accounted for on the basis of the effects of vibration and cardiac thrust. Vascular injury from these sources may stimulate fibrin production and the release of lipids which form the typical arteriosclerotic lesion.

Lipometabolic Theory

The following is a discussion of the factors in support of the theory that arteriosclerosis results from abnormalities of fat metabolism or other metabolic diseases (28).

Cholesterol in Atheromatous Lesions: Windaus noted that

arteriosclerotic aortic vessels contained six or seven times as much free cholesterol and over twenty times as much esterfied cholesterol as normal aortas (29). Rosenthal found that between the ages of twenty-five and seventy the amount of cholesterol in the aorta increased about ten times (30) The ratio of free to esterified cholesterol of the blood is similar to that in vascular plaques. Also, a portion of labeled ingested cholesterol has been detected in arteriosclerotic aortas (32).

Experimental Production of Atherosclerosis: Atherosclerosis has been produced in animals by elevation of plasma cholesterol (31). It is postulated that the fat in the blood filters through the intima but is unable to pass the high resistance of the internal elastic lamella This results in subintimal accumulation of the fats with atheroma formation. The smaller fat particles which may pass through the internal elastic membrane traverse the media and are picked up by the vessels of the adventitia and are returned to the blood stream (33, 34).

Relation of Experimental Disease to Human Arteriosclerosis: In rabbits the earliest alterations occur in the thoracic aorta about the origins of the great vessels and later the posterior thoracic wall is involved about the origins of the intercostal arteries This is in contrast to the location in man in which lesions of the abdominal aorta are common. The dog, on a high cholesterol diet with thiouracil, develops arteriosclerosis in the abdominal aorta similar to man (35). In severe atherosclerotic cholesterol fed animals thrombosis is rare but thrombosis is common in humans. In rabbits after cholesterol feeding is stopped the fat disappears from the aorta when the lesions have been present for a short time but in the older lesions a fibrous plaque remains There is no definite evidence of such reversibility in man (28). In animals the pulmonary arterial system is involved as frequently as the systemic system but in man pulmonary arteriosclerosis occurs mainly when pulmonary hypertension is present. In rabbits involvement of cerebral and retinal arteries is not common; however, this is a common site of involvement in man Lesions at these locations have been observed in the dog with a high cholesterol diet and thiouracil (35). Permeability studies on the rabbit aorta show that cholesterol can pass through the excised

aorta when normal human pressure levels are present in the vessel (36).

Increased Incidence of Atherosclerosis in Clinical States: Nephrosis, familial hyperlipemia and familial hypercholesteremia are characterized by an increase in blood fat levels and an increased incidence of coronary artery disease and arteriosclerosis. Prolonged biliary obstruction, hypothyroidism and diabetes mellitus show a poorer correlation between blood cholesterol and atherosclerosis. Familial hyperlipemia and hypercholesteremia have a high incidence of arteriosclerosis and the lesions occur in the peripheral as well as in the abdominal aorta Plaques may be found in various internal organs as well as on the eyelids and tendons. Genetic studies have implied that heterozygous groups of individuals who have varying degrees of hypercholesteremia have a susceptibility to arteriosclerosis. It has been shown that diabetic patients with hypercholesteremia are fifteen times as likely to develop arteriosclerosis as diabetic patients with normal blood cholesterols (37). Generally, however, diabetics under good control show neither hypercholesteremia nor hyperlipemia. Many diabetic patients exhibit vascular disease without abnormalities of the fat pattern. The abnormality appears to reside primarily in the arterioles and capillaries. Involvement of the glomerulus of the kidney with a disturbance of polysaccharide metabolism and ground substance of the basement membrane of the arteries is common (38).

Plasma Cholesterol: Early workers were unable to establish a relationship between hyperchloesteremia and arteriosclerosis. More recent studies have shown a relationship employing statistical techniques; however the correlation is only fair (39).

Cholesterol Phospholipid Ratios: These have been employed because the ratio correlates with the presence of arteriosclerosis. This work was carried out in animals but has not been confirmed with certainty in humans. A low ratio (relatively high phospholipid with respect to the cholesterol) is thought to prevent the deposition of the cholesterol in the vessel wall A high phospholipid with respect to the amount of cholesterol is said to maintain the cholesterol in a soluble form.

Low Density Class of Lipoproteins: Gofman in 1950 announced that there was a close correlation between the Sf (Svedbreg flotation) 12–100 molecules and arteriosclerosis of the coronary arteries (40). Patterson failed to obtain a correlation between coronary arteriosclerosis and various blood fats. He took the ante mortum serum levels of cholesterol and the Sf12–20 lipoproteins along with cholesterol phospholipid ratios and compared these figures with the degree of arteriosclerosis and fat content of human coronary arteries after death (41).

Intake of Dietary Fat and the Incidence of Atherosclerosis: The low incidence of fat intake and the rarity of advanced atherosclerosis has been described among Northern Chinese, Okinawans, Costa Ricans, Eskimos and Bantus. Aschoff reported a sharp diminution of atherosclerosis in Germany following World War I when a low intake of fat was common. Also in Norway in World War II there was a sharp reduction in mortality and morbidity from coronary atherosclerosis presumably due to the great reduction in fat and cholesterol in the diet at that time. The incidence rapidly rose following restoration of a more normal food intake. Studies of this sort are difficult to evaluate because of the numerous complicating factors such as race, stress, tobacco and other living habits.

Endocrine Factors—Gonads: There is a higher incidence of arteriosclerosis in males than in females when diabetes and hypertension are excluded. The incidence and severity of coronary atherosclerosis in bilaterally oophorectomized women is greater than in control females and is approximately equal to that of men. Also the incidence was lower in men treated with estrogen for carcinoma of the prostate than in normals. Estrogen inhibits the development of cholesterol induced coronary atherosclerosis in cockerels and estrogens were capable of reversing coronary atherosclerosis induced experimentally by cholesterol feeding in these animals. Estrogen fed to survivors of acute myocardial infarction showed a lowering of beta lipoprotein, lowering of cholesterol, an increase in phospholipids with a fall in the cholesterol phospholipid ratio (1.02 to 0.72).

Thyroid: If the thyroid is removed from a dog and it is given high cholesterol feeding arteriosclerosis results. Thyroid admin-

istration inhibits experimental atherosclerosis in cholesterol fed dogs, rabbits and chicks. Therapeutic doses of thyroid uniformly lower serum cholesterol and the atherogenic index. With clinical hyperthyroidism there is increased intestinal excretion of cholesterol and increased synthesis of cholesterol by the liver however, plasma cholesterol is diminished as the rate of secretion exceeds the rate of synthesis.

Adrenal Cortex: Cortisone administration has been followed by hyperlipemia and hypercholesteremia. ACTH and a high cholesterol feeding have produced arteriosclerosis in dogs. An increased deposition of lipids in the intima and media of the aorta has been noted in children who had received cortisone or corticotropin.

Filtration Theory

This states that the fat and protein elements of the blood are selectively filtered out of the blood stream because of the pressure in the artery, the size of the particles and the size of the gaps in the endothelium of the artery. The evidence in support of this theory has been discussed elsewhere (1).

Inflammatory Theory

This theory postulates that infections, allergic states and toxic factors are important determinants of arteriosclerosis. The evidence in support of this theory is slight.

ATHEROSCLEROSIS

This is a disease of the intima, subintima and media characterized by plaque formation and thrombosis of arteries. The arteries involved usually are the abdominal aorta, thoracic aorta, coronary arteries, cerebral and renal arteries. The arterioles and capillaries are not generally affected.

History: The first description of atheromata was made by Crell and Von Haller in the middle of the 18th century who described the lesions of atherosclerosis in detail (42).

Age, Sex and Race: Usually atherosclerosis occurs between the ages of twenty and fifty; however all ages are affected. When hemodynamic abnormalities are present, for example a patent

ductus arteriosus or coarctation of the aorta, atherosclerosis of the arch of the aorta may be present at birth. Well developed atherosclerotic plaques, once formed, apparently are irreversible and scars remain until death. Males are affected at an earlier age than females; however, when diabetes and hypertension are present atherosclerosis may occur early and at approximately the same age in both sexes. The white race is affected more than some groups of the black race (Bantu). The Chinese, Navajos and Okinawans have a lower incidence of atherosclerosis than does the white race (43, 44, 45, 46).

Pathology of Atherosclerosis: The earliest changes seen in the vessels are yellow translucent spots (hyalin) under the endothelium which are 1 or 2 mm in diameter. Later these plaques enlarge and become 1 or 2 cm in size. With progression of the disease, fat droplets consisting of cholesterol esters and other fats appear between cells of the subintima causing the intercellular substance to become loose These fatty deposits extend inwardly to the endothelium and outwardly to the media (38). With accumulation of fat under the endothelium, stretching of the endothelium occurs with ulceration of the plaque. It is probable that thrombin is liberated on the ulcerated surface which is followed by thrombosis. Fibrosis and calcification of the plaque occur. Usually the atheroma does not invade the media; however the media becomes thin behind the plaque.

History and Physical Examination: In the early stages atherosclerosis is asymptomatic In the later stages when narrowing or obliteration of vessels occurs symptoms are common. The presenting complaint is usually pain in the legs on walking (intermittent claudication), chest pain (angina pectoris), coldness of the extremities, ulceration of the tissues or visual disturbances. The common findings are diminished pulsations of vessels, such as the dorsalis pedis and posterior tibial arteries; coldness of the extremities and evidence of atherosclerotic changes in the retinal arteries which includes tortuosity, increased light reflexes, arteriovenous compression and irregularity of the arterial wall.

Laboratory Work: Atherosclerosis can be demonstrated in the aorta radiologically by a chest plate which shows calcification, usually in the aortic arch and by a plate of the abdomen which

shows calcification in the abdominal aorta. X-rays of the legs may show spotty calcification, indicating atherosclerosis (figure 205). The electrocardiogram characteristically shows evidence of a myocardial infarct or coronary insufficiency. The latter may manifest itself as inverted T waves in lead V3 or V4 (anterior coronary insufficiency) or in lead aVf (posterior coronary insufficiency). Other electrocardiographic findings, such as depression of the S-T segments in lead V4 with exercise or with acute attacks of chest pain also suggest coronary atherosclerosis.

Vascular studies show low rounded pulsations in the toes with obstructive atherosclerosis of the aorta, femoral, tibial or digital arteries. Abnormalities of the pulse height and form are important early signs of vascular disease and have proved of value in revealing early evidence of vascular disease in young diabetic patients and in patients with certain types of hypercholesteremia Other signs of atherosclerosis are low blood pressures at the ankles, compared with the wrists and low blood flows of the toes as shown with a venous congestion test (figures 135, 136, 137, 138, 139, 140, 141, 142, 143).

Various studies of the plasma fats and lipoproteins have been correlated with the presence of atherosclerosis. For the most part the correlations have been made between the plasma fats and coronary artery disease and little attention has been paid to peripheral arterial disease. Because of the uncertain position of these studies as diagnostic aids in these individuals they will be mentioned only briefly here.

Blood Cholesterol. The normal content of cholesterol in the blood is close to its saturation point so that deposition of cholesterol on the arterial wall may follow slight elevations above normal values (47) The normal values for blood cholesterols are uncertain but probably range between 150 and 250 mg per cent in Caucasians. The normal values may vary somewhat depending upon the method employed. Some patients with diabetes and myxedema have high blood cholesterol and atherosclerosis. The members of certain families run high cholesterols and have a high mortality at an early age Repeatedly, however, atherosclerosis is observed in the form of coronary disease or peripheral arterial disease in patients with normal blood cholesterols.

Cholesterol Phospholipid Ratio: Ahrens and Kunkel (48) have suggested that the cholesterol phospholipid ratio is an index of the stability of cholesterol in the blood. Cholesterol alone is insoluble in aqueous solutions but the presence of phospholipid tends to maintain cholesterol in a soluble form thereby preventing its deposition in the arterial walls. In man when the ratio is below 1 the stability of the cholesterol in the blood is good. When greater than 1 it is poor. This ratio has been correlated with the presence of experimental atherosclerosis in dogs.

Plasma Lipoproteins: Most techniques for determining lipoproteins utilize organic solvents which precipitate the protein and extract the lipids. These may be identified by salt fractionation of the plasma proteins, paper electrophoresis, alcohol fractionation or sedimentation in the ultracentrifuge.

SALT FRACTIONATION OF PLASMA: Plasma albumin can be separated from globulins by precipitation with ammonium sulfate and the globulins can be separated into euglobulin, pseudoglobulin I and pseudoglobulin II. The alpha and beta lipoproteins are associated with pseudoglobulins.

ELECTROPHORESIS: Paper electrophoresis may be used to separate the various plasma proteins (49, 50). The proteins with different electric charges travel in an electric field at different rates of speed. In this way albumin, alpha globulin, beta globulin and gamma globulin are differentiated. The alpha and beta lipoproteins are the lipoproteins which migrate with the same speed as the alpha and beta globulins. They are designated alpha I and beta I lipoproteins. It has been found that with atherosclerosis the beta lipoproteins are usually high. In some cases the cholesterol has been removed from the alpha and beta lipoprotein complexes and their relative amounts compared. With atherosclerosis the beta lipoprotein cholesterol is high compared with the alpha lipoprotein cholesterol. This relationship is shown by a ratio of beta to alpha lipoprotein cholesterol. A high ratio suggests atherosclerosis. The ratio can be normalized with estrogens.

ALCOHOL FRACTIONATION: The Cohn method of fractionation utilizes the variable solubility of various protein fractions in different concentrations of ethel alcohol at low temperatures and at various acid concentrations (51). Five fractions can be obtained.

Fraction V contains plasma albumin; fraction IV alpha I globulin (and alpha I lipoprotein); fraction III contains beta I globulin (and beta I lipoprotein). About 25 per cent of the total cholesterol in humans forms part of the alpha lipoprotein and about 75 per cent of the total cholesterol is found in beta lipoproteins (52).

ULTRACENTRIFUGE: With this technique a strong gravitational force is applied which separates the lipoproteins according to their molecular weights and the specific gravity of the solution employed. The lipoproteins are designated in Sf units (Svedberg flotation units), one unit denotes a migration rate of 10^{-13} cm per second per dyne per gram.* A lipoprotein which migrates at ten times the above rate of speed is identified as a lipoprotein of the Sf 10 class. Gofman found a high correlation between Sf class 12–20 lipoproteins and clinical coronary atherosclerosis (53, 54). There is some correlation also between Sf class 20–200 and atherosclerosis. The concentrations of both of these classes of molecules are greater in males than in females, also they increase with age and in patients with a history of coronary occlusion and with the experimental production of atherosclerosis in rabbits. The correlation between these measurements and atherosclerosis was reported to be two to four times as great as with serum cholesterol.

Diagnosis: This is based on finding evidence of atherosclerosis in the retinal and peripheral arteries, using opthalmoscopic, x-ray or plethysmographic techniques and possibly by demonstrating a high blood cholesterol, relatively low phospholipid, high beta lipoprotein or a predominance of the Sf 12–20 or 20–200 lipoproteins in the blood.

Differential Diagnosis: Diabetes, myxedema, familial hypercholesteremia, xanthomatotic hypercholesteremia, and essential hyperlipemia should be differentiated from idiopathic atherosclerosis.

Diabetes is characterized by vascular lesions in small vessels such as capillaries, arterioles and venules which are evident as capillary aneurysms in the eye and as renal glomerulosclerosis.

* A dyne is the force which will produce an acceleration of 1 cm per second per second in a gram mass ($F = ma$) where m is mass in grams and a is acceleration in cm per second² and F is in dynes.

Neuritis, abnormal blood sugar, glucose tolerance tests and ketosis may be present.

Myxedema is characterized by a typical clinical picture of dry, wrinkled skin with sparse hair, sensitivity to cold, low iodine uptake and blood iodine and high blood cholesterol.

Familial hypercholesteremia is characterized by a high blood cholesterol, evidence of arteriosclerosis in the electrocardiogram or elsewhere with a family history of coronary occlusions at early ages.

Xanthomatotic hypercholesteremia is characterized by fatty plaques around the eyes, tendons or in the skin, often with high blood cholesterol and evidence of arteriosclerosis in retinal arteries and in the electrocardiogram.

Essential Hyperlipemia. These patients are characterized by a milky serum. Beta lipoproteins in the blood are high. Blood cholesterol may or may not be high. There is a slightly increased incidence of arteriosclerosis. Fatty deposits may be present in the skin or tendons.

Treatment: Clinical impressions and statistical data suggest that weight reduction is beneficial for longevity; however, there is no definite evidence to show that weight reduction favorably retards atherosclerosis. A diet low in calories and in animal fats probably is desirable. Although the relationship between the blood cholesterol and arteriosclerosis in man has not been established with certainty, it seems the better part of judgment at this time to advise a low cholesterol diet until further knowledge is available. Kempner (55) was able to reduce the blood cholesterol in patients with high blood cholesterols an average of 27 per cent with a rice diet. The high cholesterol foods which generally are avoided on a low cholesterol diet are: brain, liver, heart, kidneys, sweetbreads, fish, fish roe, animal fats (such as pork, bacon, lard) salmon, mackeral, dark tuna, oysters, egg yolks, dairy products such as whole milk, cream cheese, cheese spreads, butter, ice cream, salad dressing, rich gravies, cream soups, waffles, coffee cakes, muffins, doughnuts, desserts and other foods made with cream or egg yolks.

Unsaturated Fats: Recently it has been shown that oils containing high quantities of unsaturated fats, such as safflower oil, suc-

cessfully lower blood cholesterol. Corn oil (Mazola) has a similar effect (56). The usual dose of safflower oil emulsion (Saff®*) is one ounce twice daily. The drug is usually given with breakfast and supper. It is possible for patients to maintain a fairly normal diet and still lower their blood cholesterols with this agent. The absorption of cholesterol from the intestinal tract is not retarded by these oils but it is possible that they facilitate the removal of cholesterol from the blood stream by the liver and hasten the intestinal excretion of this agent. The exact mechanism of action is under investigation at this time

Beta Sitosterol (Cytellin®): This agent has been effective in lowering the blood cholesterol in man (57). The usual dose is one tablespoonful before each meal Small doses have been effective in lowering the blood cholesterol in chicks and in decreasing the incidence of atherosclerosis in cholesterol fed rabbits The agent acts by forming a 1 to 1 molecular complex with cholesterol thereby preventing the absorption of cholesterol from the gastrointestinal tract. It will be recalled that under ordinary circumstances fat is absorbed by lymphatics into the intestinal tract. It is transported in combination with the blood proteins to the liver where part of it is excreted into the intestinal tract through the bile duct. The cholesterol ordinarily is again absorbed from the intestinal tract. Beta sitosterol may reduce endogenous cholesterol by interfering with the reabsorption of cholesterol during the hepato-intestinal cycle.

Thyroid Preparations: Thyroid is employed because of experimental evidence which shows that arteriosclerosis in animals can be prevented by thyroid administration and because of the increased incidence of atherosclerosis in patients with hypothyroidism (58). Triiodothyronine (Cytomel®†) is an effective agent for lowering the blood cholesterol in patients with normal or elevated cholesterols. In a series of twenty-five patients studied by the author, a 17 per cent fall in cholesterol was obtained in patients who had moderate elevations of their blood cholesterols. Triiodothyroacetate (Triac®) also lowers cholesterol rather satis-

* Abbott Pharmaceutical Company.

† Smith, Kline and French Pharmaceutical Company

factorily; however, there was more tendency for tolerance to develop with this agent than occurred with Cytomel®. Other thyroid preparations may have a somewhat similar effect; however they have not been studied extensively in hypercholesteremic patients with normal thyroid function. Thyroid and its derivatives are generally contraindicated in patients with angina pectoris or recent myocardial infarcts; however, in patients with chronic healed myocardial infarcts without angina pectoris this form of treatment may be attempted carefully.

Estrogens: These have been effective in lowering cholesterol and beta lipoproteins in man (59) and in improving atherosclerosis in chicks. Most currently available estrogens are not suitable for male subjects because of the side effects which include depression, fatigue, irritability, impotence, loss of libido and gynecomastia. It is highly probable that non-feminizing estrogens which are capable of lowering blood cholesterol will be available in the near future. These agents will be valuable aids in the treatment of hypercholesteremia and atherosclerosis.

Lipotropic Agents: Because the lipotropic substances (choline, methionine and inositol) constitute an important part of the phospholipids, it was theorized that they might aid in keeping the cholesterol in the blood in a stable form. *It is felt that these* agents are ineffective in the treatment of coronary atherosclerosis.

Heparin: This has been used for atherosclerosis because of its ability to clear the plasma following its injection. A treatment scheme of 200 mg subcutaneously twice weekly has been suggested; however there is no convincing evidence that this improves atherosclerosis.

Detergents: Surface active detergents have been employed; however they have generally not been effective in controlling atherosclerosis.

ATHEROSCLEROSIS OBLITERANS

Arteriosclerosis Obliterans

Atherosclerosis obliterans is an obstructive degenerative arteropathy which is characterized by occlusion of arteries by atheromata and or by superimposed thrombus (60).

Age, Sex, Race and Etiology: This is similar to atherosclerosis.

Pathology: Atherosclerosis obliterans commonly involves the bifurcation of the aorta, iliac, femoral, popliteal, anterior tibial and posterior tibial arteries and less commonly involves the ulnar arteries. The pathologic lesion which is present is usually that of atherosclerosis or atherosclerosis combined with medial arteriosclerosis (60, 61). A thrombus adherent to an intimal plaque is common. The thrombus may occur in several layers before occlusion is complete. It may be gray or red. Calcareous deposits often are present at the base of the atheroma or in the medial coat of the artery (62). The atheroma contains neutral fat, cholesterol and fibrous tissue. Fragmentation of the internal elastic layer beneath the atheromatous plaque is common.

History and Physical Examination: The symptoms may be slow in onset or they may appear suddenly, as when thrombosis is superimposed on atherosclerotic lesions. Often a history of old as well as recent arterial disease is present

Pain: Intermittent claudication is an early sign of ischemia to the muscles. It may involve the foot, calf, thigh, hip or back depending upon the site of the lesion. Pain at rest is a sign of more advanced disease. It is relieved somewhat by sitting up with the feet in the dependent position or by rubbing the feet slightly. Pain associated with ulcers may be severe in diabetic patients with nerve irritation or it may be painless in the absence of ulcers when neuropathy is advanced and sensory nerves are destroyed. The pain of ischemic neuritis results from ischemia of nerve trunks and often is associated with shooting pains which follow the distribution of the peripheral nerves (64). Nerve root irritation may result from ischemia. The pain of diabetic neuritis may exist as a soreness of muscle groups which is aggravated often by exercise. The pain is not relieved immediately with rest as is the pain of intermittent claudication. Pain of disuse may occur when patients lie with the limb in one position for long periods of time. This often is associated with stiffness of joints and muscular weakness.

Sensitivity to Cold: This is seen often in the early stages of vascular disease. Blanching of the digits may occur from a cool or cold environment with or without the other color changes which are characteristic of the Raynaud's phenomenon.

Paresthesias: These result frequently from ischemic neuropathy in the form of a dead sensation, tingling, prickling, burning or coldness of the limbs or digits. In diabetic patients certain toes may be analgesic. These toes may be warm and show evidence of interruption of sympathetic nerves.

Decreased Pulsations: Absent or diminished pulsations of the femoral, popliteal, dorsalis pedis or posterior tibial arteries as compared with similar arteries in the upper extremities are reliable signs of arterial disease. It is important always to compare the pulsations in the upper with those in the lower extremities. With arteriosclerosis disease of the lower extremities with diminution in pulsations is common while pulsations often are normal in the upper *extremities.*

Murmurs: Murmurs over the abdominal aorta and iliac arteries occur with narrowing of these vessels or with aneurysmal dilatations Murmurs are absent when the vessels are occluded completely. The murmurs may appear with exercise and disappear with rest.

Color of Tissues: The color of the limbs depends upon the state of the circulation and on the position of the part. With the legs at heart level and with mild disease the color may be pale. With diabetes the skin color is slightly yellow due in some cases to increased yellow pigment (carotin) in the skin. With more advanced disease ecchymotic areas may occur. When capillary or venular dilatation is present from ischemic atony, the color may be slightly cyanotic.

Posture: When the legs are elevated the tissues become waxy white in early cases. In more advanced cases mottled discoloration occurs which is due to extravasation of red cells into the tissues in which case the color does not disappear and then reappear by manual pressure and release of pressure on the ecchymotic area (figure 294). After elevation and dependency the part becomes cherry red (figure 316). The length of time for the development of the cherry red color is related to the intensity of the disease.

Temperature: The temperature of the involved part usually is lower than the uninvolved part (figure 248) unless infection is present or sympathetic nerves are interrupted in which case the temperatures may be higher. The temperature of the part is not

a good indication of the amount of disease which is present as the temperature is often normal in the presence of arterial disease.

Ulceration and Gangrene: Obvious tissue deterioration with ulceration, gangrene and infection may occur. The ulcers are present often on the tips of the toes, the heel, internal malleolus, dorsum of the foot and at pressure points (figure 299).

Infections: These are common and are caused usually by the Micrococcus pyogenes and anaerobic organisms such as the Clostridium perfringens. Other pyogenic organisms may be present also. These organisms produce a purulent discharge and inhibit healing. Osteoporosis, edema and atrophy of muscles may be present.

Laboratory Tests: The following tests are indicated:

Glucose Tolerance Test: This is done to rule out diabetes.

VDRL This is performed to rule out lues.

Red Blood Count: This is done to rule out polycythemia

Plasma Fat Studies· These should be made to search for hypercholesteremia and hyperlipemia. The following studies are often abnormally high especially in young patients with arteriosclerosis. The normal range will be given: Cholesterol: 150–250 mg per cent; cholesterol/phospholipid ratio: 0 7–1.3; neutral fat: 0–200 mg per cent; total lipids: 450–1800 mg per cent; beta lipoprotein cholesterol; increased. The following blood fats tend to be low with atherosclerosis: total phospholipids as lecithin; normal value 175–350; alpha lipoprotein cholesterol and alpha/beta lipoprotein cholesterol ratio.

Electrocardiograms and Teleoroentgenograms are obtained to evaluate the cardiac status especially if surgery is contemplated

Ophthalmoscopic Examination is carried out to determine the presence and amount of arteriosclerosis and the presence of capillary aneurysms which suggest diabetes (figures 264, 267)

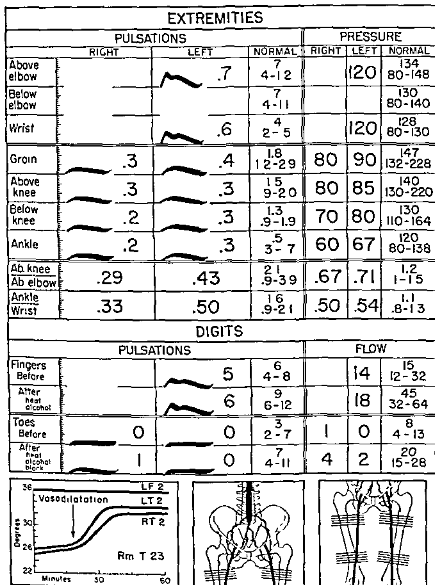
Vascular Examination: This is carried out: 1) to determine the presence of arterial disease; 2) to locate obstructions within the arterial tree; 3) to determine the amount of functional arteriolar vasoconstriction, and 4) to determine the amount of collateral circulation. It is important to perform these tests before surgical procedures so that comparative measurements can be made after

surgery. The post surgical and follow-up plethysmograms usually make post-surgical aortograms unnecessary.

Soft Tissue X-rays: Postero-anterior and lateral views of the abdominal aorta may show calcification of the arteries (figure 206). The transverse diameter of the abdominal aorta may be increased (aneurysm) or decreased (atherosclerosis) due to the process of arteriosclerosis. X-rays of the iliac, common femoral, distal femoral and popliteal region may show: 1) spotty calcified atheromatous lesions which may be associated with occlusion of arteries (figure 205), or 2) diffuse calcification of the vessel which often appears as a series of transverse rings (figure 204) (*Moenckeberg sclerosis*) (61). This usually is not associated with arterial obstruction as the intima generally is not involved.

Clinical Types: CHRONIC OBSTRUCTION OF THE BIFURCATION OF THE AORTA (LERICHE SYNDROME) (figure 346): There is a gradual onset of bilateral intermittent claudication which is felt in the hips, thighs, calves and feet. The femoral, popliteal, posterior tibial and dorsalis pedis pulses are decreased with normal pulses in the brachial, radial and ulnar arteries. If good collateral circulation is present the tissues are not atrophic and there is no elevational pallor or dependent rubor.

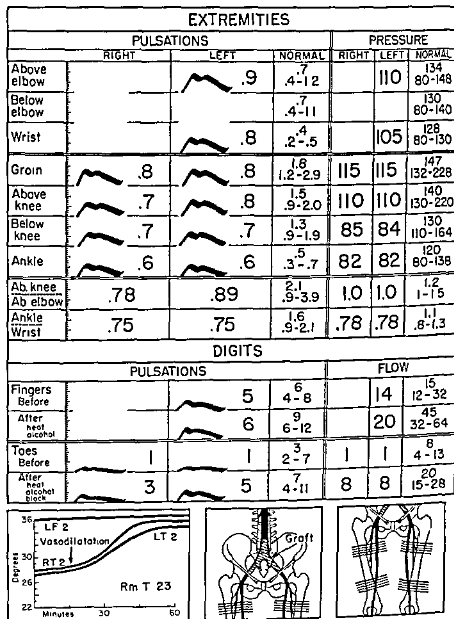
Vascular Examination (figures 319, 320): The pulses at the groins and at distal points on the lower extremities are low and rounded compared with those of the upper extremities. The pulsation indexes indicate low pulsations of the lower extremities as compared with the upper. The systolic blood pressures of the lower extremities from the groin to the ankles are low as compared with similar points on the upper extremities. The blood pressure indexes are low indicating relative lowering of the blood pressure in the lower extremities. Good collateral circulation around the obstruction here is present as shown by systolic blood pressure measurements at the ankles which are the same before as after manual compression of the femoral artery. The small blood vessels distal to the site of the obstruction are relatively normal as shown by nearly normal pulsations, blood flow and skin temperatures of the toes after a posterior tibial nerve block. Sympathetic vasoconstrictor tone may be high as shown by a large increase in pulsations, blood flow and skin temperature after a



EXTREMITIES	PULSATIONS			PRESSURE		
	RIGHT	LEFT	NORMAL	RIGHT	LEFT	NORMAL
Above elbow		.7	7 4-12		120	134 80-148
Below elbow			7 4-11			130 80-140
Wrist		.6	4 2-5		120	128 80-130
Groin	.3	.4	1.8 1.2-2.9	80	90	147 132-228
Above knee	.3	.3	1.5 .9-2.0	80	85	140 130-220
Below knee	.2	.3	1.3 .9-1.9	70	80	130 110-164
Ankle	.2	.3	.5 3-7	60	67	120 80-138
Ab. knee / Ab elbow	.29	.43	2.1 .9-3.9	.67	.71	1.2 1-1.5
Ankle / Wrist	.33	.50	1.6 .9-2.1	.50	.54	1.1 .8-1.3

DIGITS	PULSATIONS			FLOW		
Fingers Before		5	6 4-8		14	15 12-32
After heat alcohol		6	9 6-12		18	45 32-64
Toes Before	0	0	3 2-7	1	0	8 4-13
After heat alcohol block	1	0	7 4-11	4	2	20 15-28

Figure 319. Vascular study and aortogram of a forty-three year old female with chronic obstruction of the bifurcation of the aorta (Leriche syndrome) before surgery (see text for explanation).



EXTREMITIES

	Pulsations Right	Pulsations Left	Pulsations Normal	Pressure Right	Pressure Left	Pressure Normal
Above elbow		.9	.7 .4-1.2		110	134 80-148
Below elbow			.7 .4-1.1			130 80-140
Wrist		.8	.4 .2-.5		105	128 80-130
Groin	.8	.8	1.8 1.2-2.9	115	115	147 132-228
Above knee	.7	.8	1.5 .9-2.0	110	110	140 130-220
Below knee	.7	.7	1.3 .9-1.9	85	84	130 110-164
Ankle	.6	.6	.5 .3-.7	82	82	120 80-138
Ab. knee / Ab elbow	.78	.89	2.1 .9-3.9	1.0	1.0	1.2 1-1.5
Ankle / Wrist	.75	.75	1.6 .9-2.1	.78	.78	1.1 .8-1.3

DIGITS

	Pulsations Right	Pulsations Left	Pulsations Normal	Flow Right	Flow Left	Flow Normal
Fingers Before		5	6 4-8		14	15 12-32
After heat alcohol		6	9 6-12		20	45 32-64
Toes Before	1	1	3 2-7	1	1	8 4-13
After heat alcohol block	3	5	7 4-11	8	8	20 15-28

Figure 320. Vascular study carried out one month after surgery performed by Dr Michael De Bakey. The abdominal aorta was resected and an arterial homograph was placed as shown in the figure. The postoperative vascular study made it unnecessary to repeat the aortogram Same patient as figure 319.

posterior tibial nerve block. Soft tissue x-rays of the region of the bifurcation of the aorta show spotty calcification of the aorta which is consistent with atherosclerosis (figure 205).

Unilateral Iliac Artery Obstruction: Intermittent claudication is present and may involve the hip if the hypogastric artery is obstructed also. Diminished pulsations are present in the femoral and distal arteries. Elevational pallor and dependent rubor may or may not be present depending upon the amount of collateral circulation which is present.

Vascular Examination (figures 321, 322): This reveals low pulsations and systolic blood pressures at the groin and at all distal points of the lower extremity as compared with the normal leg and as compared with the upper extremities. The pulsation and systolic blood pressure indexes are abnormal on the abnormal side as compared with the normal side (index-lower/upper). The height of the pulse, blood flow and skin temperature of the toe on the diseased side are low especially if there is arterial disease distal to the iliac artery obstruction or if the sympathetic vasoconstrictor tone is high. In the latter case the circulation increases significantly after a posterior tibial nerve block.

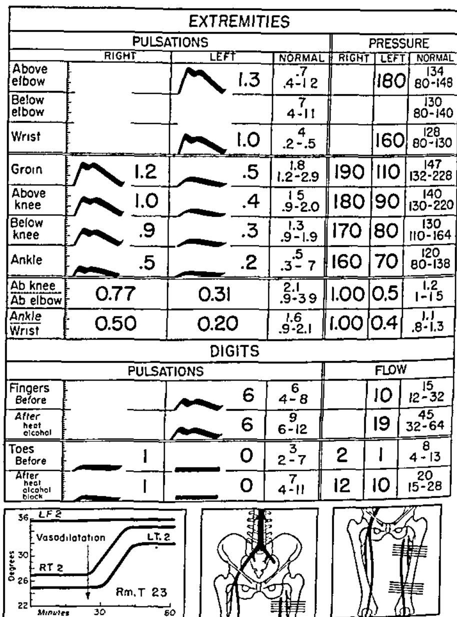
Obstruction of Common Femoral Artery. This is difficult to differentiate from obstruction of the iliac artery without an aortogram which usually shows the upper and lower limits of the lesion clearly

Superficial Femoral Artery, Upper Portion (figure 323): This is a common lesion and is characterized by palpable femoral artery pulses with diminished pulses distally

Obstruction to the Deep Femoral Artery: Thigh claudication is present without calf claudication. An aortogram is helpful in diagnosing this lesion. A soft tissue x-ray may show atheromatous type of calcification in the region of this artery.

Plethysmographic examination shows diminished thigh pulses with normal pulses distally.

Obstruction in the Distal Third of the Superficial Femoral Artery· This is in the region of the adductor canal. Intermittent claudication is present beginning at or below the knee. Good femoral pulses are present but are absent in the popliteal, posterior tibial and dorsalis pedis arteries. The appearance of the



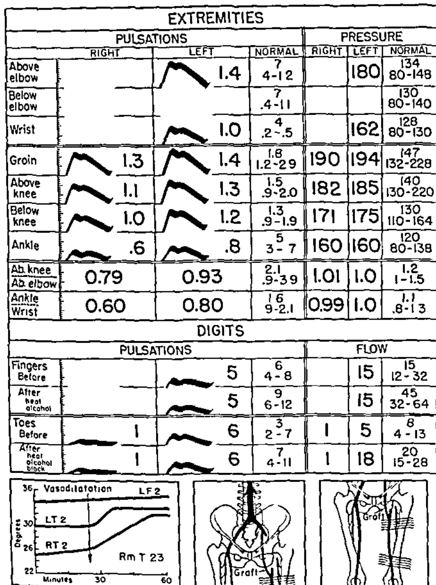
EXTREMITIES

	PULSATIONS Right	PULSATIONS Left	PULSATIONS Normal	PRESSURE Right	PRESSURE Left	PRESSURE Normal
Above elbow		1.3	.7 .4-1.2		180	134 80-148
Below elbow			7 4-11			130 80-140
Wrist		1.0	4 .2-.5		160	128 80-130
Groin	1.2	.5	1.8 1.2-2.9	190	110	147 132-228
Above knee	1.0	.4	1 5 .9-2.0	180	90	140 130-220
Below knee	.9	.3	1.3 .9-1.9	170	80	130 110-164
Ankle	.5	.2	.5 .3-7	160	70	120 80-138
Ab knee / Ab elbow	0.77	0.31	2.1 .9-3.9	1.00	0.5	1.2 1-1.5
Ankle / Wrist	0.50	0.20	1.6 .9-2.1	1.00	0.4	1.1 .8-1.3

DIGITS

	PULSATIONS Right	PULSATIONS Left	PULSATIONS Normal	FLOW Right	FLOW Left	FLOW Normal
Fingers Before		6	6 4-8		10	15 12-32
After heat alcohol		6	9 6-12		19	45 32-64
Toes Before	1	0	3 2-7	2	1	8 4-13
After heat alcohol block	1	0	7 4-11	12	10	20 15-28

Figure 321. A forty-eight year old male with unilateral external iliac artery obstruction. Record made before surgery (see text for explanation). From the *American Journal of Surgery*



EXTREMITIES	PULSATIONS RIGHT	PULSATIONS LEFT	PULSATIONS NORMAL	PRESSURE RIGHT	PRESSURE LEFT	PRESSURE NORMAL
Above elbow		1.4	7 4-12		180	134 80-148
Below elbow			7 .4-11			130 80-140
Wrist		1.0	4 .2-.5		162	128 80-130
Groin	1.3	1.4	1.8 1.2-2.9	190	194	147 132-228
Above knee	1.1	1.3	1.5 .9-2.0	182	185	140 130-220
Below knee	1.0	1.2	1.3 .9-1.9	171	175	130 110-164
Ankle	.6	.8	5 3-7	160	160	120 80-138
Ab. knee / Ab. elbow	0.79	0.93	2.1 .9-3.9	1.01	1.0	1.2 1-1.5
Ankle / Wrist	0.60	0.80	1.6 9-2.1	0.99	1.0	1.1 .8-1.3

DIGITS	PULSATIONS			FLOW		
Fingers Before		5	6 4-8		15	15 12-32
After heat alcohol		5	9 6-12		15	45 32-64
Toes Before	1	6	3 2-7	1	5	8 4-13
After heat alcohol block	1	6	7 4-11	1	18	20 15-28

Figure 322 Same patient as figure 321 after surgery by Dr. J. Howard Payne. An arterial bypass homograph was placed as shown. Vascular studies showed marked improvement after surgery. Reproduced with permission of the *American Journal of Surgery*

tissues and the presence or absence of elevational pallor or dependent rubor depends upon the amount of collateral circulation present around the knee.

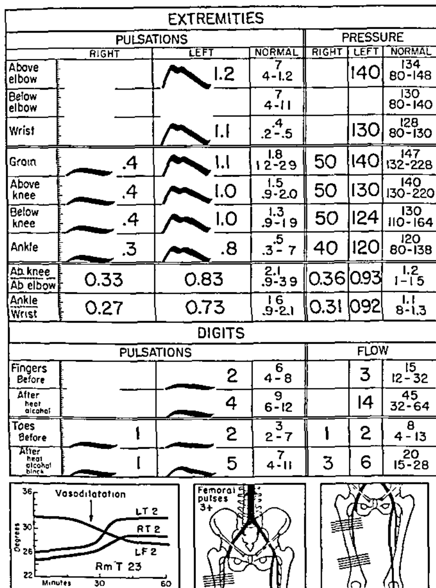
Vascular Examination (figures 324, 325): This shows increased pulsations and blood pressures above the obstruction with decreases below the obstruction. The patency of the distal blood vessels is judged by the height of the pulsations, blood flow and skin temperature of the digit. When they are patent and when there is good collateral circulation around the knee there is a large increase in the circulation of the toe after a posterior tibial nerve block. The lesion is usually shown by aortogram or by a femoral arteriogram.

OBSTRUCTION TO POPLITEAL ARTERY: Intermittent claudication is present below but not above the knee.

Vascular Examination (figures 326, 327): This shows large pulsations and blood pressures at the groin and above the knee with low pulsations below the knee and at the ankle. The pulsations, blood flow and skin temperatures after a posterior tibial nerve block depend upon the amount of collateral circulation around the knee and the amount of organic arterial disease distal to the obstruction.

OBSTRUCTION OF ANTERIOR TIBIAL OR POSTERIOR TIBIAL ARTERIES: Intermittent claudication often of the foot is present and the posterior tibial and dorsalis pedis artery pulses are absent or diminished.

Vascular Examination. This shows sharp decreases in pulsations and blood pressures from the ankle cuff with abnormal pulsation and blood pressure indexes. Pulsations, blood flow and *skin temperatures of the toe are often small before* and after vasodilatation produced by a posterior tibial nerve block. The relative patency of the dorsalis pedis and posterior tibial arteries can be assayed by measuring the pulsations of the toe: 1) before and after manual compression of the posterior tibial artery which measures the circulation through the dorsalis pedis, and 2) before and after manual compression of the dorsalis pedis artery which measures the circulation through the posterior tibial artery (figures 183, 187).



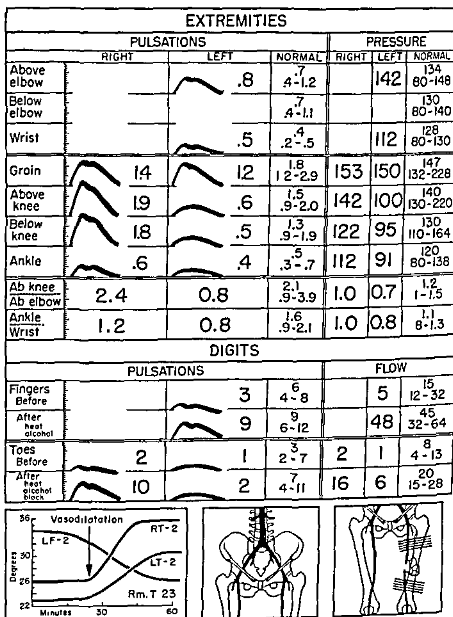
EXTREMITIES

	Pulsations Right	Pulsations Left	Pulsations Normal	Pressure Right	Pressure Left	Pressure Normal
Above elbow		1.2	7 4-1.2		140	134 80-148
Below elbow			7 4-11			130 80-140
Wrist		1.1	.4 .2-.5		130	128 80-130
Groin	.4	1.1	1.8 1.2-2.9	50	140	147 132-228
Above knee	.4	1.0	1.5 .9-2.0	50	130	140 130-220
Below knee	.4	1.0	1.3 .9-1.9	50	124	130 110-164
Ankle	.3	.8	.5 .3-.7	40	120	120 80-138
Ab. knee / Ab elbow	0.33	0.83	2.1 .9-3.9	0.36	0.93	1.2 1-1.5
Ankle / Wrist	0.27	0.73	1.6 .9-2.1	0.31	0.92	1.1 .8-1.3

DIGITS

	Pulsations Right	Pulsations Left	Pulsations Normal	Flow Right	Flow Left	Flow Normal
Fingers Before		2	6 4-8		3	15 12-32
After heat alcohol		4	9 6-12		14	45 32-64
Toes Before	1	2	3 2-7	1	2	8 4-13
After heat alcohol block	1	5	7 4-11	3	6	20 15-28

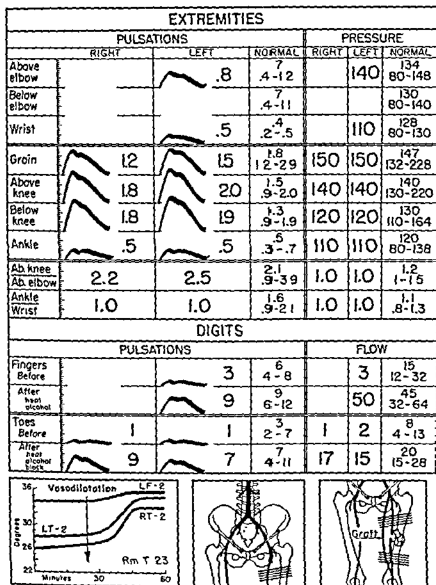
Figure 323 Vascular and aortographic studies in a patient with an obstruction in the upper portion of the superficial femoral artery. The low pulsations, blood pressures, pulsations of the toes, skin temperatures and blood flow on the right as compared with the left are apparent. The low pulses and pressures begin with the cuff at the right groin and are present at all points distally.



EXTREMITIES	PULSATIONS RIGHT	PULSATIONS LEFT	PULSATIONS NORMAL	PRESSURE RIGHT	PRESSURE LEFT	PRESSURE NORMAL
Above elbow		.8	.7 .4-1.2		142	134 80-148
Below elbow			.7 .4-1.1			130 80-140
Wrist		.5	.4 .2-.5		112	128 80-130
Groin	1.4	1.2	1.8 1.2-2.9	153	150	147 132-228
Above knee	1.9	.6	1.5 .9-2.0	142	100	140 130-220
Below knee	1.8	.5	1.3 .9-1.9	122	95	130 110-164
Ankle	.6	.4	.5 .3-.7	112	91	120 80-138
Ab knee / Ab elbow	2.4	0.8	2.1 .9-3.9	1.0	0.7	1.2 1-1.5
Ankle / Wrist	1.2	0.8	1.6 .9-2.1	1.0	0.8	1.1 .8-1.3

DIGITS	PULSATIONS RIGHT	PULSATIONS LEFT	PULSATIONS NORMAL	FLOW RIGHT	FLOW LEFT	FLOW NORMAL
Fingers Before		3	6 4-8		5	15 12-32
After heat alcohol		9	9 6-12		48	45 32-64
Toes Before	2	1	3 2-7	2	1	8 4-13
After heat alcohol block	10	2	7 4-11	16	6	20 15-28

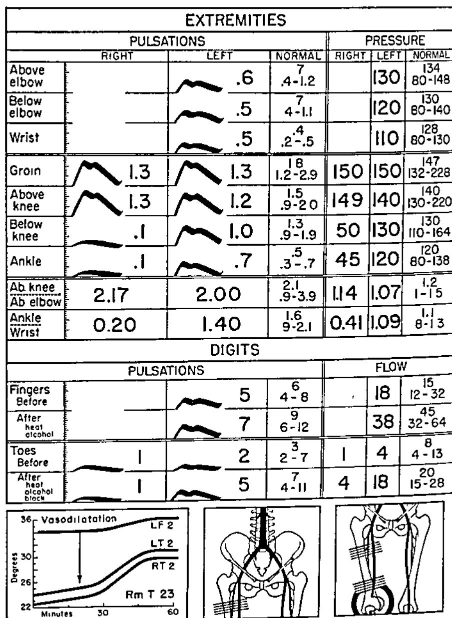
Figure 324. Typical vascular and aortographic studies in a patient with *an obstruction in the distal third of the superficial femoral artery on the left* (see text for explanation).



EXTREMITIES	PULSATIONS Right	PULSATIONS Left	PULSATIONS Normal	PRESSURE Right	PRESSURE Left	PRESSURE Normal
Above elbow		.8	7 .4-1.2		140	134 80-148
Below elbow			7 .4-1.1			130 80-140
Wrist		.5	.4 .2-.5		110	128 80-130
Groin	1.2	1.5	1.8 1.2-2.9	150	150	147 132-228
Above knee	1.8	2.0	1.5 .9-2.0	140	140	140 130-220
Below knee	1.8	1.9	1.3 .9-1.9	120	120	130 110-164
Ankle	.5	.5	.5 .3-.7	110	110	120 80-138
Ab. knee / Ab. elbow	2.2	2.5	2.1 .9-3.9	1.0	1.0	1.2 1-1.5
Ankle / Wrist	1.0	1.0	1.6 .9-2.1	1.0	1.0	1.1 .8-1.3

DIGITS	PULSATIONS Right	PULSATIONS Left	PULSATIONS Normal	FLOW Right	FLOW Left	FLOW Normal
Fingers Before		3	6 4-8		3	15 12-32
After heat alcohol		9	9 6-12		50	45 32-64
Toes Before	1	1	3 2-7	1	2	8 4-13
After heat alcohol block	9	7	7 4-11	17	15	20 15-28

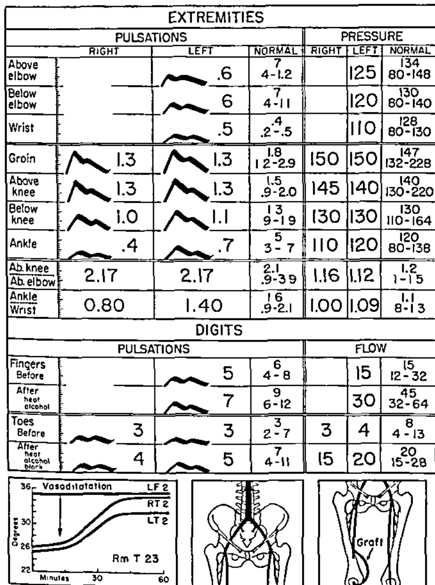
Figure 325. Same patient as figure 324 after surgery by Dr. J. Howard Payne. An arterial bypass homograph was placed as shown in the figure. The pulsations and blood pressures in the left leg above the knee and at all points distally have improved. The form of the pulse waves and blood flow at the left toe have improved also.



EXTREMITIES	PULSATIONS Right	PULSATIONS Left	PULSATIONS Normal	PRESSURE Right	PRESSURE Left	PRESSURE Normal
Above elbow		.6	7 .4-1.2		130	134 80-148
Below elbow		.5	7 4-1.1		120	130 80-140
Wrist		.5	.4 .2-.5		110	128 80-130
Groin	1.3	1.3	1 8 1.2-2.9	150	150	147 132-228
Above knee	1.3	1.2	1.5 .9-2 0	149	140	140 130-220
Below knee	.1	1.0	1.3 .9-1.9	50	130	130 110-164
Ankle	.1	.7	.5 .3-.7	45	120	120 80-138
Ab knee / Ab elbow	2.17	2.00	2.1 .9-3.9	1.14	1.07	1.2 1-1 5
Ankle / Wrist	0.20	1.40	1.6 9-2.1	0.41	1.09	1.1 8-1 3

DIGITS	PULSATIONS Right	PULSATIONS Left	PULSATIONS Normal	FLOW Right	FLOW Left	FLOW Normal
Fingers Before		5	6 4-8		18	15 12-32
After heat alcohol		7	9 6-12		38	45 32-64
Toes Before	1	2	3 2-7	1	4	8 4-13
After heat alcohol block	1	5	7 4-11	4	18	20 15-28

Figure 326 A sixty year old male with a chronic obstruction in the right popliteal artery The vascular studies show increased pulsations of normal form above the obstruction with decreased pulsations of abnormal form below the obstruction Normal circulation is present in the left leg



EXTREMITIES						
	PULSATIONS			PRESSURE		
	RIGHT	LEFT	NORMAL	RIGHT	LEFT	NORMAL
Above elbow		.6	7 4-1.2		125	134 80-148
Below elbow		6	7 4-11		120	130 80-140
Wrist		.5	.4 .2-.5		110	128 80-130
Groin	1.3	1.3	1.8 1 2-2.9	150	150	147 132-228
Above knee	1.3	1.3	1.5 .9-2.0	145	140	140 130-220
Below knee	1.0	1.1	1 3 9-1 9	130	130	130 110-164
Ankle	.4	.7	5 3-7	110	120	120 80-138
Ab. knee / Ab. elbow	2.17	2.17	2.1 .9-3 9	1.16	1.12	1.2 1-1 5
Ankle / Wrist	0.80	1.40	1 6 .9-2.1	1.00	1.09	1.1 8-1 3
DIGITS						
	PULSATIONS			FLOW		
Fingers Before		5	6 4-8		15	15 12-32
After heat alcohol		7	9 6-12		30	45 32-64
Toes Before	3	3	3 2-7	3	4	8 4-13
After heat alcohol block	4	5	7 4-11	15	20	20 15-28

Figure 327. Vascular study after placement of a bypass graft in the patient shown in figure 326.

OBSTRUCTION TO DIGITAL ARTERIES OF TOES: All available palpable vessels pulsate normally.

Vascular Examination (figure 328): This shows normal pulsations and blood pressures of the extremities. Examination of the digits shows low pulses, blood flow and skin temperatures. With organic disease, there is no significant increase after a posterior tibial nerve block; with sympathetic vasoconstriction, the pulses, flow and temperatures increase markedly after this procedure. Digital artery obstructions are not uncommon with diabetes.

SUBCLAVIAN ARTERY OBSTRUCTION: The patient complains of *pain in the arm. Here the pulsations and systolic blood pressures* are reduced on the diseased side which is more common on the left than on the right. The circulation measured at the finger is dependent upon the amount of collateral circulation which is *present around the obstruction.*

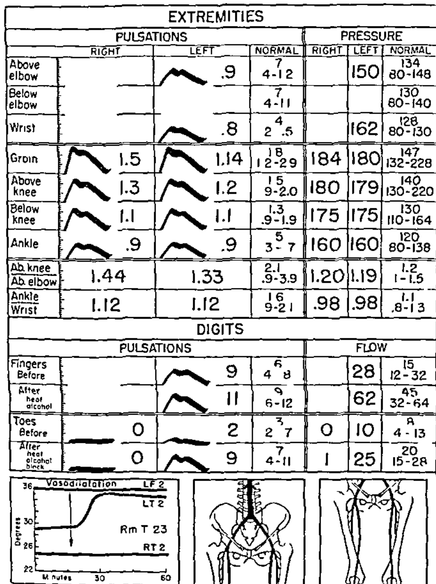
Vascular Examination. This shows evidence of decreased circulation below the site of the obstruction.

Treatment: This is the same as outlined for atherosclerosis but in addition the following is carried out.

Anticoagulants: These drugs may be indicated on theoretic grounds in advanced cases where blood flow is sluggish and there is a tendency for thrombosis. Anticoagulants are indicated in acute arterial thrombosis.

Vasodilatation: This can be induced often by a combination of drugs and procedures. These include a warm environment, covering of the part to prevent evaporation, alcohol orally two or three times a day if there are no contraindications, Priscoline® 25 mg three or four times a day, Roniacol® 50 mg three or four times a day and Dibenzyline® 5 to 10 mg three times a day. The patient should avoid emotional disturbances and should stop the use of tobacco.

Lumbar Sympathectomy: This is advisable when: 1) the disease state is primarily functional, 2) the posterior tibial nerve block indicates a strong sympathetic vasoconstrictor tone with nearly normal digital flow after the block, and 3) when it is desirable to increase the circulation to the skin of the distal third of the extremity (64). Sympathectomy is not effective in producing a



EXTREMITIES						
	PULSATIONS			PRESSURE		
	RIGHT	LEFT	NORMAL	RIGHT	LEFT	NORMAL
Above elbow		.9	7 4-12		150	134 80-148
Below elbow			7 4-11			130 80-140
Wrist		.8	4 2 .5		162	128 80-130
Groin	1.5	1.14	18 12-29	184	180	147 132-228
Above knee	1.3	1.2	15 9-2.0	180	179	140 130-220
Below knee	1.1	1.1	1.3 .9-1.9	175	175	130 110-164
Ankle	.9	.9	5 3 - 7	160	160	120 80-138
Ab. knee / Ab. elbow	1.44	1.33	2.1 .9-3.9	1.20	1.19	1.2 1-1.5
Ankle / Wrist	1.12	1.12	16 9-21	.98	.98	1.1 .8-13
DIGITS						
	PULSATIONS			FLOW		
Fingers Before		9	6 4 8		28	15 12-32
After heat alcohol		11	9 6-12		62	45 32-64
Toes Before	0	2	3 2 7	0	10	8 4 - 13
After heat alcohol block	0	9	7 4-11	1	25	20 15-28

Figure 328. A forty-eight year old male with thromboangiitis obliterans with obstruction to digital arteries of the right second toe. The disease process was organic as no significant increase in circulation to the toe was produced after a posterior tibial nerve block.

significant increase in circulation to the muscle and walking distance is increased only slightly in a small percentage of patients with this procedure (65, 66).

Sympathetic Block With Injection of Alcohol: This often produces a neuritis and is seldom employed.

Postural Exercises (figure 401): These may be helpful; however the elevational aspect of Buerger's exercises is undesirable because of the ischemia which is produced. The oscillating bed is useful in healing skin ulcers when maximum vasodilatation is produced first by surgical sympathectomy or other measures (67).

Systemic Drugs. Antibiotics are employed for secondary infection which is usually caused by Bacillus pyocyaneous or other pyogenic organisms. Cultures should be made. Penicillin is usually effective.

Vitamins: Ischemic neuritis is difficult to improve when due to arteriosclerosis in the absence of diabetes. Neuritis may be improved somewhat however with vitamin B 12 and B complex parenterally if the neuritis is not of long standing.

Local Treatment: Crusts and debris should be removed if possible. This can be performed best with warm, wet dressings of boric acid solution Local trypsin (Tryptar®) or streptokinase and streptodornase (Varidase®) may be employed for this purpose. Ointments, especially those containing local anesthetic agents may increase tissue necrosis and should not be employed. Oil base ointments are less desirable than water base vehicles. Rarely surgical debridement is indicated. Fluid under pressure should be removed Neo-Polycin® is a useful local antibiotic because of its wide spectrum and its non-greasy base. Excessive heat and prolonged soaks producing maceration should be avoided.

Skin Grafts: These at times may be of value.

Insulin: Diabetes should be rigidly controlled.

Phlebotomy: Polycythemia vera if present should be controlled by repeated bleeding of 500 cc of blood or by the use of radioactive phosphorous.

Amputations (figures 432–435): With digital artery disease a single digit may be amputated. When more than one digit is

diseased, a transmetatarsal amputation may be indicated. If the vascular examination indicates good circulation below the knee, a below knee amputation may be indicated. If not, the amputation is usually done above the knee.

Thromboendarterectomy or Graft: Occlusion of the bifurcation of the aorta (Leriche syndrome) is satisfactorily treated by either of these procedures. Arterial homografts usually are effective. Plastic prostheses are effective also. These procedures characteristically eliminate intermittent claudication.

Iliac Artery Obstruction: Thromboendarterectomy or arterial homografts are usually effective. If the obstruction is long a by-pass graft from aorta to femoral artery may be employed (68, 69).

Common Femoral Artery Obstruction: A thromboendarterectomy may be sufficient or an arterial homograft may be used (70, 71).

Obstruction of Distal Portion of Femoral Artery: When the lesion is at or above Hunter's canal a by-pass graft may be effective or a thromboendarterectomy may be performed (72, 73).

Popliteal Artery Obstruction: Surgery in this location is more difficult as the artery is small and collateral circulation may be interrupted (74). A thromboendarterectomy, arterial or vein graft is possible in some cases (75, 76). A sympathectomy is done generally, especially if the obstruction involves the bifurcation of the popliteal artery.

MEDIAL ARTERIOSCLEROSIS

(Monckeberg's Arteriosclerosis)

This is a disease of the media of muscular arteries characterized by medial calcification without significant involvement of the intima (61).

Age and Sex: The age ranges from twenty-seven to sixty-nine years and males are involved more frequently than females in a ratio of 60 to 1.

Etiology: This is unknown, however it has been suggested that damage to the media and repair by calcification may be a cause. Infection, congenital syphilis, renal disease, hypervitaminosis D, and hyperparathyroidism have been considered etiologies

Pathology: The abnormality is confined primarily to the media

of muscular arteries which shows calcareous deposits, fibrosis, focal necrosis and cystic degeneration. The intima and adventitia are not generally involved (77). The calcification forms rings around the artery similar to tracheal cartilage and involves long sections of the arterial tree. The arteries of the legs are involved more frequently than those of the arms. As the disease progresses the arteries increase in diameter and length, lose their elasticity, become tortuous and the walls become thin and aneurysmal where the vessel wall has been weakened.

History and Physical Examination: There are very few symptoms. Intermittent claudication, coldness of the skin, atrophy or swelling of the tissues and ulceration usually are absent. Leg cramps at rest occur in about one-third of the cases. The physical examination is essentially normal. Typically the dorsalis pedis and posterior tibial arteries pulsate normally. There are no murmurs over the aorta, femoral or other arteries.

Laboratory Work: Soft tissue x-rays of the aorta, femoral, popliteal and tibial arteries reveal typical dense, uniform calcification which often extends throughout the entire length of the artery (figure 204). The calcium appears to be deposited in transverse lines giving the appearance of a chain of rings (77). This is in contrast to the calcification in intimal atherosclerosis which is patchy, dispersed and tends to be deposited in the long axis of the blood vessel. Vascular studies are essentially normal in uncomplicated cases of medial arteriosclerosis. When intimal atherosclerosis is present as well the vascular studies are abnormal.

Prognosis: Thrombosis of the blood vessels of the extremities ordinarily does not occur and there is little tendency to develop impairment of the circulation. This is in contrast to intimal atherosclerosis which often goes on to progressive occlusion of the blood vessels and carries an unfavorable prognosis.

Treatment: Treatment for night cramps such as calcium lactate orally, Benadryl, quinidine sulfate or quinine usually relieve symptoms. Excessive intake of vitamin D should be stopped. It is possible that disodium versenate would be effective in removing the calcium from the vessels; however this form of treatment is not yet established.

ARTERIOLOSCLEROSIS AND HYPERTENSIVE ISCHEMIC ULCERATION

Arteriolosclerosis

Arteriolosclerosis is a symptom complex consisting of thickening of the walls of the arterioles which is usually associated with an elevated blood pressure (47).

Etiology: Arteriolosclerosis often is associated with essential hypertension but may be secondary to hypertension due to other causes such as 1) renal disease; for example glomerulonephritis, pyelonephritis, polycystic kidneys, 2) endocrine diseases, such as Cushing's syndrome, pheochromocytoma, 3) vascular diseases, such as coarctation of the aorta, 4) porphyria or 5) cerebral diseases, such as a brain tumor or bulbar poliomyelitis.

Age, Sex and Race: Arteriolosclerosis is uncommon before the age of twenty. About fifty per cent of the patients beyond fifty years of age suffer from this condition (78). Arteriolosclerosis is slightly more common in females than in males. The disease is rare in Negroes in Africa but is common in Negroes in America who have a higher incidence of this disease than do whites. Similar observations have been made in the Chinese who emigrate to the United States. The disease is rare in Indians in the Southwestern portions of the United States. Hypertension is said to be inherited as a dominant characteristic.

Pathology: Arteriolosclerosis involves the vessels of the kidney, muscles and brain (79, 80). Arteriolosclerosis occurs in cerebral vessels, coronary arteries, retinal vessels and arterioles supplying striate muscle. Cerebral thrombosis or hemorrhage, coronary thrombosis, retinal hemorrhages, congestive heart failure and uremia may occur when arteriolosclerosis is advanced.

History and Physical Examination: The history may be that of palpitation, headaches, weakness of the arms and legs or shortness of breath. The physical examination may reveal neurologic findings of a cerebral vascular accident, evidence of left ventricular congestive heart failure, cardiac enlargement or myocardial infarction.

Diagnosis: This is based on the finding of Grade II eye grounds which is associated with elevated blood pressure along with a typical clinical picture.

Differential Diagnosis: Arteriolosclerosis associated with essential hypertension should be differentiated from: arteriolosclerosis associated with coarctation of the aorta in which the blood pressure is high in the arms and low in the legs; pheochromocytoma which is associated with a positive Regitine and histamine test; Cushing's syndrome which is associated with moon-face, hypertension, purple striae, glycosuria and often an adrenal cortical tumor; periarteritis nodosa which shows fibrinoid degeneration in the arterioles of a muscle biopsy; arteriosclerosis of the aorta which is characterized by high systolic pressure but essentially normal diastolic pressure; neurogenic hypertension which shows paroxysms of elevated systolic pressures with normal diastolic pressures without clinical evidence of arteriosclerosis (normal eye grounds).

Laboratory Work: The electrocardiogram often shows typical left ventricular strain pattern with tall R waves in lead V4 with negative J shifts and inverted T waves in this lead. In early cases renal function tests may be diminished slightly, but later albuminuria, uremia and elevated non-protein nitrogen is present. X-ray of the chest shows rounding of the heart at the apex often with congestion of the lungs.

Treatment: This is directed toward lowering of the blood pressure including the use of rauwolfia and its derivatives such as reserpine, deserpidine, the alseroxylon fraction of rauwolfia serpentina and the crude root. Also hydralazine (Apresoline®), ganglionic blocking agents such as pentolinium (Ansolysen®) and chlorothiazide (Diuril®). Rauwolfia and Apresoline lower pressure through a central blocking action of the sympathetic nervous system. Ganglionic blocking agents interrupt the autonomic nervous system at the level of ganglia such as the paravertebral ganglia. Chlorothiazide causes the excretion of sodium and chloride in about equal quantities and hastens removal of excess fluid from the body. All of these agents can be used to advantage in combination.

Hypertensive Ischemic Ulceration

This is a syndrome consisting of hypertension, local ulcers and necrotizing arteriolitis.

Age and Sex: The condition is a little more common in women than in men. The age is usually from fifty to seventy years.

Etiology: The ulceration is associated with severe hypertension which usually is of unknown etiology.

Pathology: Organic degenerative changes are present in the arterioles There is thickening of the arteriolar wall with a decrease in the size of the lumen of the vessels (81–82). Hyalin degeneration of the media with intimal proliferation and periarteritis may be present (figure 264). Thrombosis of small vessels may occur. Similar changes occur in arteries in hypertensive patients who do not have ischemic ulcers (83). Only the small arteries and arterioles are involved.

History and Physical Examination: The patient complains of tenderness and ulceration of the legs. The lesions may be initiated by trauma. An ulcer on the lateral or posterolateral aspect of the lower third of the leg is common. The lesion usually varies in size from 1 to 5 centimeters in diameter. Secondary infection is unusual. A thick membranous scar may form over the ulcer.

Laboratory Work: The blood pressure is or has been elevated, often to high levels. Biopsy of various skin areas shows intimal and medial thickening of the vessel wall. Vascular examination shows an increased peripheral resistance

Course: Healing occurs slowly requiring many months.

Treatment: Peripheral vasodilators, Roniacol®, Priscoline®, and Dibenzyline® may be tried. A lumbar sympathectomy could be carried out to improve the cutaneous circulation.

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Figure 329. Leo Buerger 1879–1943. Born in Vienna; graduated from Columbia University, College of Physicians and Surgeons in 1901. Professor of urologic surgery at the New York Polyclinic in 1917 and later professor of urology at the College of Medical Evangelists in Los Angeles. Although he devised many urologic operating instruments he is remembered for his descriptions of thromboangiitis obliterans.

CHAPTER 30

Thromboangiitis Obliterans

THROMBOANGIITIS obliterans is an organic granulomatous inflammatory disease of the arteries, veins and nerves often associated with arterial obstruction and gangrene of tissues.

History: Buerger, in 1908, was the first to report on a large series of patients with this entity although isolated instances of the condition had been reported previously by others (1, 2)

Sex, Race and Age: The disease involves males in a ratio of about 99 to 1 (3, 4). The Jewish race is affected somewhat more commonly than others although the racial difference is not great. There is no hereditary tendency although the disease is seen occasionally in siblings. The disease has been described in Chinese, Japanese, Koreans, Turks and in a few Negroes. The disease usually occurs between the ages of twenty and forty years.

Etiology: This is unknown. The following have been suggested as etiologic factors: virus and fungus infections, increased coagulability of the blood, hemo-concentration, increased production of male hormone and tobacco. There is a low incidence of this disease among non-smokers and a high incidence among heavy smokers. Often improvement follows the cessation of smoking; however many patients continue to have exacerbations of the disease even if they do not smoke. It is possible that some patients may be sensitive to tobacco and develop lesions of thromboangiitis obliterans after many years of smoking (5). Cold and nervousness are aggravating factors.

Gross Pathology: The anterior and posterior tibial, radial and ulnar, palmar and digital arteries are affected commonly. The brachial and femoral arteries may be affected late in the course of the disease (2, 6, 7). Grossly the arteries are contracted and hard, and the lumens are occluded by an adherent mass. The arteries

and veins may be bound together by inflammatory tissue and both may be obstructed. On slitting the artery longitudinally it is apparent that the obstruction is present segmentally. Occasionally two obstructions are present in the same vessel; often the vessel is patent between.

Microscopic Pathology (figure 330): In the acute stage there is a panarteritis with nonspecific vascular granulation tissue extending from intima to periadventitial tissue which is composed of lymphocytes, histocytes, plasma cells and an occasional giant cell. Usually an early thrombus is present In the subacute stage the thrombus becomes recanalized and merges with the thickened inflamed intima The internal elastic membrane is not disrupted and aneurysms are absent. In the chronic stage the thrombus becomes sclerotic and the internal elastic lamina is especially prominent. In this stage dense fibrous tissue encloses the arteries, veins and nerves The most striking feature is the extensive proliferation of endothelial and fibroblastic cells in all coats of the artery with thrombus formation in the lumen. The vessel is not occluded by proliferation of the intima alone Atheromata, irregular thinning and calcification of the media is not found as occurs in atherosclerosis. Simple arterial thrombosis or embolism does not show the marked fibrosis of the clot or of the media and adventitia as occurs in thromboangiitis obliterans.

History and Physical Examination: The usual presenting symptom is pain (8). Typically this consists of intermittent claudication involving the calf or arch of the foot. Pain may be present at rest when ischemic neuritis is present. Local pain and tenderness may be present in superficial veins, arteries, nerves or other tissues near the inflamed vessels and nerves. Coldness of the extremities, sensory disturbances and muscular weakness occur. Other symptoms and signs are: 1) ulceration and gangrene; 2) edema; 3) thrombophlebitis; 4) cold limbs; 5) discoloration, and 6) abnormal arterial pulsations.

Ulcerations and Gangrene: Ulcers occur spontaneously or from trauma. The lesions commonly involve the digits, frequently around the margins of the nails. The gangrene may be the size of the head of a pin or involve the tip of an entire digit. Gangrene

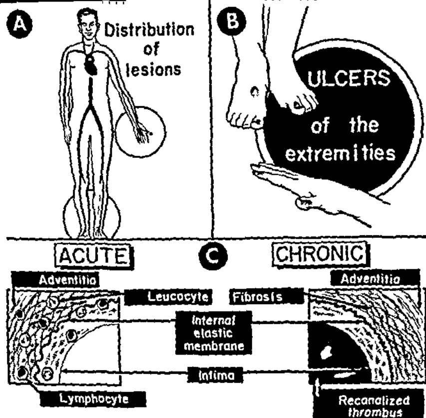


Figure 330 Typical clinical and pathologic findings in patients with thromboangiitis obliterans

of a foot is not uncommon but gangrene of the leg is rare. The gangrene is wet if venous obstruction or infection is present.

Edema: This often is present and is due to: 1) capillary dilatation from ischemia; 2) prolonged dependency; 3) venous obstruction, or 4) lymphangiitis.

Thrombophlebitis: This is of the migrating type and occurs in superficial veins in a significant percentage of patients. The saphenous veins are involved frequently and the iliofemoral and

axillary veins are involved less commonly. Often small subcutaneous veins are involved by small venous thrombi 1 to 3 cm in diameter. These appear as nodules which appear in crops, last a few weeks, are tender during this period after which the tenderness leaves, however the nodules remain

Cold Limbs: Coldness of a finger or a hand suggests organic arterial disease, especially if the coldness is persistent.

Arterial Pulsations: Absence of radial or ulnar pulsations is strongly suggestive of thromboangiitis obliterans. Usually the pulsations of the posterior tibial and dorsalis pedis arteries are not palpable. Pulsations of the femoral and popliteal arteries usually are present.

Discoloration. Color changes of the skin of the digits of a hand or foot are common. With elevation the part becomes pale and with dependency it becomes red (figure 316).

Laboratory: Plethysmographic, hematologic and radiologic studies are of importance in diagnosis.

The Vascular Examination· The pulsations and systolic blood pressures are often normal immediately above the elbows or knees and are frequently abnormal at the ankles, wrists, toes or fingers. With the patient in a warm environment differences in the temperature of individual digits are present often, which is a sign of local arterial disease (figure 248). Tests for blood flow in individual arteries may be carried out in the hand by compressing the radial or ulnar artery and noting the effects on the pulsations measured at the hand or finger (9) (figures 181, 182). Obstruction of the dorsalis pedis or posterior tibial arteries may be located in a similar fashion (figures 183, 184) Measurement of the potential blood flow is useful for predicting the possible vasodilating effect of various types of therapy, for example sympathectomy.

Blood Tests Hematocrit determinations and serologic tests for syphilis, blood sugars and blood cholesterols should be carried out to rule out polycythemia, syphilis, diabetes and hypercholesteremia (10, 11).

X-rays of the Extremities These often show osteoporosis (figure 209). The digital arteries usually are not calcified as they are with arteriosclerosis obliterans A moth-eaten appearance of the bones suggests osteoporosis on the basis of arterial ischemia.

whereas a generalized decalcification suggests osteoporosis due to disuse.

Diagnosis: This is based upon the finding of organic arterial disease of one or more digits, usually in a male under forty years of age with a history of migrating superficial thrombophlebitis. The diagnosis is aided by typical microscopic sections of the diseased area, however biopsy is not ordinarily performed because of slow healing of the wound. Microscopic sections should always be made if amputation becomes necessary.

Treatment: *Tobacco:* It is generally conceded that tobacco is harmful in patients with thromboangiitis obliterans. At times it is well to test this point by making thermometric or plethysmographic studies of the circulation before and after smoking (figures 185, 247). In this way individual differences in tobacco sensitivity can be observed and more accurate advice regarding smoking can be given (5, 12, 13)

Sympathectomy: Upper thoracic or lumbar preganglionic sympathectomy produces clinical and laboratory evidence of improvement in a significant percentage of patients when they have been properly selected by means of a vasodilating technique with plethysmographic or thermometric observations (figure 249). Sympathectomy is of special value in this disease because of the vasodilatation which is produced in the distal portions of the extremities where disease is commonly located (14, 15).

Vasodilating Agents: Alcohol, Priscoline®, Roniacol® and Dibenzyline® employed in combination are useful vasodilators.

Steroids: Prednisone has been advocated for the acute stages of the disease. Hydrocortisone sodium succinate intravenously (Solu-Cortef®) may be effective when active arteritis is present.

Mechanical Methods: The Sander's bed is of some value in healing skin ulcers (figure 422). Intermittent venous occlusion, the Pavex boot and other similar devices are of little value or may be harmful in certain cases.

Anticoagulant Therapy: This may be employed during the acute stage of the disease when arterial thrombosis is common

Antibiotics: These are employed for local or systemic infections and are given during steroid therapy to prevent spread of infection.

Amputation: This is delayed as long as possible, often allowing

gangrenous parts to slough spontaneously. The determination of the necessity to amputate is aided by plethysmographic study (figures 432–435).

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CHAPTER 31

Arteritis

Arteritis is an inflammatory process of arteries caused by diseases of various etiologies. The diseases included under this category are temporal arteritis, nonsuppurative nodular panniculitis, disseminated arteritis, nodular vasculitis, erythema induratum, erythema nodosum, infectious arteritis, allergic angiitis, non-specific arteritis, and pulseless disease.

TEMPORAL ARTERITIS

Cranial Arteritis

This is an inflammatory disease of the temporal and other arteries of unknown cause.

History: The disease was described in 1890 by Hutchinson (1) and was named in 1932 by Horton, Magath and Brown (2).

Etiology: This is not generally known; however infection, arteriosclerosis, allergy and trauma have been suggested in certain cases.

Age and Sex: The disease usually affects patients over fifty-five years of age and there is no sex predilection.

Pathology (figure 331): The disease usually affects the branches of the carotid artery; however other arteries are affected less commonly The length of the arterial segments involved is usually several centimeters. The artery feels swollen and nodular. Microscopically focal collections of lymphocytes and fibroblasts are seen around the vasa vasorum and around other portions of the artery. The pathology is that of a segmented giant cell (3, 4), tuberculoid, granulomatous reaction with central areas of fibrinoid necrosis. Fibrous intimal thickening, medial necrosis and thrombosis is present. Aneurysms (5) and eosinophiles are unusual The veins and nerves are not usually involved. The *lesions* resemble allergic angiitis.

Laboratory Findings: There may be a mild anemia and moderate leukocytosis with a shift to the left in the differential neutrophil count. The sedimentation rate is rapid. Vascular studies with an appropriate pick-up cup over the temporal artery show abnormal pulsations over the diseased segment. The pulsations usually are decreased except for a short time during the acute inflammatory stage when they are increased.

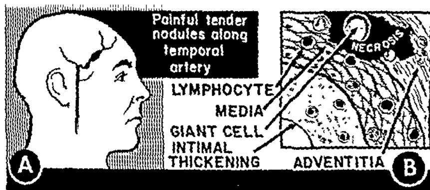


Figure 331. Clinical and pathologic findings in patients with temporal arteritis. (A) Distribution of lesions (B) Pathologic changes in artery.

History and Physical Examination: Systemic symptoms such as fever and malaise usually precede the local findings in the temporal artery by two to four weeks. Severe headache (frontal and temporal) is the main symptom which may begin unilaterally but usually becomes bilateral. Fever and night sweats are common. Cerebral symptoms such as vertigo, disorientation, delirium, diplopia, blindness or other visual disturbances may occur (5, 6, 7, 8). The temporal artery is usually tender and cordlike. Neurologic manifestations suggesting cerebral involvement may be present. Ophthalmoscopic examination may reveal the presence of optic neuritis.

Course: The disease process lasts from 2 to 30 months. The attacks often are recurrent. The mortality rate varies from 1 to 12 per cent (9). Death is due often to cerebral involvement (10).

Treatment: The most effective treatment is prednisone, prednisolone, ACTH or cortisone in large doses which is given until symptoms are controlled (11, 12, 13, 14). The anticoagulants may be employed to prevent arterial thrombosis. Salicylates help relieve pain. X-rays applied to the affected arteries or injection with procaine have been employed to relieve local distress (15). Excision of the involved artery may relieve pain. Chlortetracycline (Aureomycin®) may be effective.

NONSUPPURATIVE NODULAR PANNICULITIS

Parkes Weber-Christian Syndrome

This is a disease of unknown etiology which is characterized by a relapsing febrile course, nonsuppurative subcutaneous nodules, malaise and joint pains (16).

Age and Sex: Reportedly it is a disease of women in a ratio of 3 to 1 occurring in their second to fourth decade of life. Up to 1952, fifty-four cases had been described in the literature (17).

Pathology (figure 332): Christian (18) described "a cellular infiltration of the panniculus adiposus." Lymphocytes and leukocytes are present. Necrosis is common. Periarteritis and endarteritis may occur with thrombosis and ischemic fat necrosis (19).

Etiology: This is thought to be due to an allergy to bacteria, drugs, iodides or bromides.

History and Physical Examination: The patient complains of what appears to be an upper respiratory tract infection with malaise, joint pains, fever and nodules on the arms and legs. The nodules are prominent manifestations of disease and appear as subcutaneous tender areas similar to an incipient furuncle. They are distributed primarily on the lower extremities but are present to some extent on the arms. The face is rarely involved. Occasionally the nodules break down and discharge a yellowish fluid with fat globules. Evidence of liver disease may be present (20).

Laboratory Work: A leukopenia may be present. Biopsy often results in non-healing wounds.

Prognosis: The disease is usually not fatal but 14 fatalities have been reported, the deaths being caused by staphylococcus, tuberculosis, uremia or peritonitis (17, 21).

Differential Diagnosis: The disease must be differentiated from erythema induratum, erythema nodosum, allergic angiitis, lupus erythematosus, dermatomyositis, rheumatic nodules and traumatic fat necrosis (17, 22). Points of differentiation are as follows: The lesions of erythema induratum often are painless and ulcerate and active visceral tuberculosis is present. The lesions

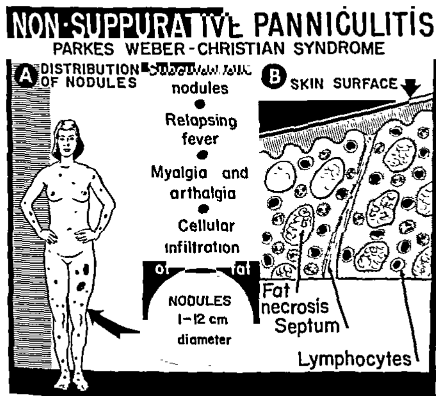


Figure 332. Clinical and pathologic findings in patients with panniculitis.

of erythema nodosum occur in crops and follow an acute disease such as coccidiomycosis or drugs such as bromides. Allergic angiitis shows eosinophilic infiltration of the tissues. Asthma and other allergies are present. Lupus erythematosus is characterized by the butterfly rash on the face, visceral lesions and the LE cell in blood tests and bone marrow. Dermatomyositis shows muscle

atrophy and atrophy of the skin. Rheumatic nodules occur in patients with rheumatic heart disease.

Treatment: Meticorten may be tried but often a relapse follows cessation of the drug. Antibiotics given for secondary infection and skin grafts may be necessary. Improvement has followed penicillin treatment. Light doses of x-ray and foreign protein therapy have produced remission in some cases. Potassium iodide may produce an exacerbation.

DISSEMINATED ARTERITIS

This is an organic vascular disease characterized by arteritis, arteriolitis and venous thrombosis which involves the small and medium sized arteries of the extremities, spinal cord or viscera (23, 24).

Sex and Age: Both sexes are affected. Young women are affected commonly.

Etiology: Unknown.

History and Physical Examination: Pain in various digits, muscle groups or organs of the body is common. Gangrene of portions of digits may occur. Fever and purpura are common. There is a progressive downhill course often with convulsions or other signs of involvement of the nervous system (25, 26).

Pathology *(figure 333):* Purpura, involvement of the arteries of the brain, spinal cord and viscera occur (24). The lesions are similar to periarteritis nodosa in that the capillaries, arterioles and venules are involved in a degenerative process which often is associated with arterial and venous thrombosis. Medial necrosis of the arteries is rare.

Laboratory Examination: Vascular studies show organic involvement of arteries of digits with or without involvement of large arteries.

Differential Diagnosis: Disseminated arteritis differs from disseminated lupus erythematosus as the former does not produce butterfly lesions of the skin or the Libman-Sack syndrome with endocardial lesions. Disseminated arteritis differs from periarteritis nodosa because medial necrosis does not occur in the former but is common in the latter.

Treatment: Similar to disseminated lupus erythematosus (Chapter 32).

Prognosis: The disease is progressive and is usually fatal.

NODULAR VASCULITIS

NONTUBERCULOUS ERYTHEMA INDURATUM

This is a nontuberculous disease characterized by nodular, usually non-ulcerative, lesions of the extremities which in other respects resembles erythema induratum (27).

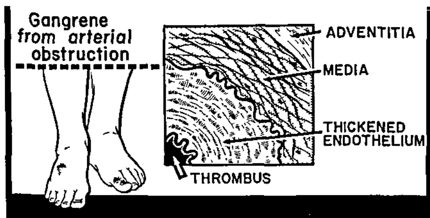


Figure 333. Clinical and pathologic findings in patients with disseminated arteritis.

Age and Sex: It occurs commonly between the ages of thirty and fifty years and women are affected more frequently than men.

Etiology: The etiology is unknown; however an allergy to an antigen has been suspected. No organism can be cultured from this lesion.

Pathology (figure 334): The lesions resemble those of erythema induratum except tubercles and tubercle bacilli are not present.

Giant cells may be present. There is endothelial proliferation, medial necrosis and periarterial fibrosis of the blood vessels.

History and Physical Examination: The usual complaint is painful nodules of the skin (28). The nodules are red and vary from a few millimeters to a few centimeters in size. They occur

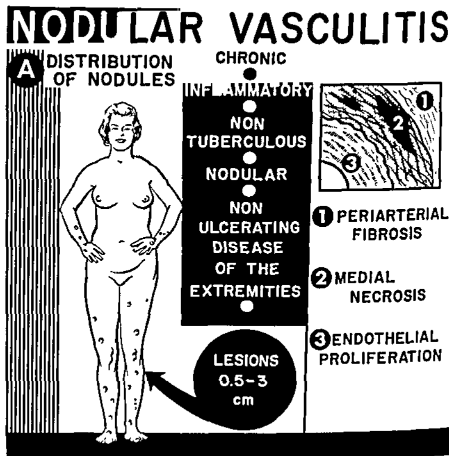


Figure 334. Clinical and pathologic findings in patients with nodular vasculitis.

in crops or singly on any part of the extremities; however they are seen commonly on the lower leg. Ulceration is rare.

Course: The lesions last often for several months.

Treatment: Prednisone should be tried but should be discontinued if improvement does not occur. Foreign protein therapy

has been effective in isolated cases Elastic bandages are helpful if edema is present.

ERYTHEMA INDURATUM

BAZIN'S DISEASE

This is a chronic disease characterized by nodular lesions of the skin and subcutaneous tissue which is associated often with tuberculosis.

Age and Sex: Females in their second decade are affected commonly; however men and boys are affected also

Etiology: The disease is often caused by active tuberculosis and is associated commonly with tuberculous lymphadenitis. In rare instances it is possible to grow the Mycobacterium tuberculosis from biopsy of the lesions.

Pathology (figure 335): The histologic changes consist of a panniculitis with tuberculoid granuloma Nonspecific endophlebitis and endarteritis of the subcutaneous tissues are common. Tubercles with giant cells may be present. Endothelial proliferation in small arteries, arterioles, venules and lymph vessels may occur along with destruction of elastic and collagenous fibers with atrophy and necrosis of fat. Periarterial fibroblastic proliferation is pronounced at times with occasional necrosis of the medial coat. The vessels may be completely destroyed or thrombosed

History and Physical Examination: The usual complaint is painful calf muscles. The symmetrical location of red nodules on the posterior aspects of the calves of the legs is suggestive of erythema induratum. The lesions are red or deep blue in the skin or subcutaneous tissue and vary from two millimeters to two or three centimeters in diameter. The nodules are symmetrical and appear in crops Necrosis and ulceration are common. After healing scars may remain. Orthostatic edema may occur. The disease occurs commonly in the winter The lesions are generally painless until they ulcerate. The ulcers are irregular with poorly defined margins and dirty gray granulating purulent bases (29).

Laboratory Work: Biopsy of lymph nodes or skin lesions and ginuea pig innoculation for tuberculosis may reveal the organism.

Differential Diagnosis: Superficial thrombophlebitis is simu-

lated because of the edema. Erythema nodosum differs in that it is a disease of short duration while erythema induratum is a disease of long duration. Tertiary syphilis is usually unilateral whereas erythema induratum is bilateral.

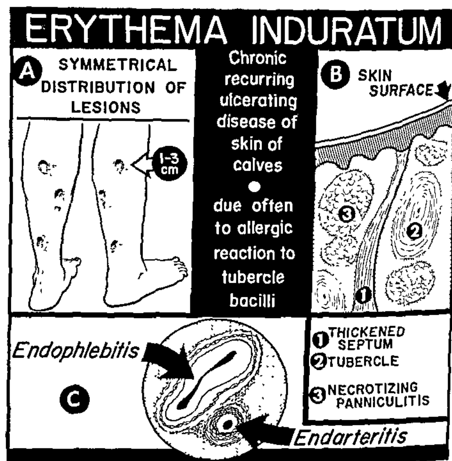


Figure 335. Clinical and pathologic findings in patients with erythema induratum

Treatment: X-ray of the tuberculous lymph glands, prolonged bed rest with elevation of the leg, applications of warm, wet packs and elastic stockings to control orthostatic edema all are helpful Streptomycin has given dramatic results (30). Isoniazid 100 mg three times a day orally should be tried (31). If toxic signs develop the dose should be cut in half. For ulceration wet dressings

with 1 per cent neomycin in distilled water may be employed or Vioform® 1 per cent in Lassar's Paste is helpful. The latter is changed daily the wound being cleaned with benzine and cotton before each application.

ERYTHEMA NODOSUM

This is an acute inflammatory nonsuppurative cutaneous disorder characterized by subcutaneous nodules of the extremities.

Sex and Age: The disease is four times more frequent in females than in males. It occurs commonly from eight to thirty-two years of age.

Etiology: This is thought to be a local sensitivity of connective tissues and blood vessels to the toxins of the staphylococcus, other bacteria or viruses. The disease is associated with rheumatic fever and may follow toxins, sulfa drugs, bromides, measles, diphtheria, leprosy, coccidioidomycosis, tuberculosis, syphilis, pharyngitis, tonsilitis, malaria, sarcodosis and Hodgkin's disease (32, 33, 34).

Pathology (figure 336): There is edema of the skin with capillary dilatation and collections of neutrophilic leukocytes and lymphocytes around arterioles and venules in the middle and lower portions of the corium. Proliferation of the endothelium of the vessels may occur.

History and Physical Examination: Nodular lesions are most common on the anterior surfaces of the legs and are less common on the thighs and arms and occur rarely on the hands and face. The trunk is involved less frequently than the limbs. The nodes are 1 to 2 cm in diameter and are firm and pink or purple. Ulceration does not occur. The disease lasts for about 6 weeks. The lesions may appear in crops. Fever, malaise and arthralgia may be present.

Laboratory: Not diagnostic.

Treatment: Offending drugs should be stopped Local hot applications may be helpful with analgesics Antihistamines and adrenal steroids may be tried. The disease is a self limited one which disappears in about six weeks even if untreated.

Differential Diagnosis: The disease should be differentiated from erythema induratum which also has a predilection for the legs; however erythema induratum involves the calves rather than

the anterior portions of the legs. The lesions of erythema induratum tend to persist and ulcerate and are associated with active tuberculosis.

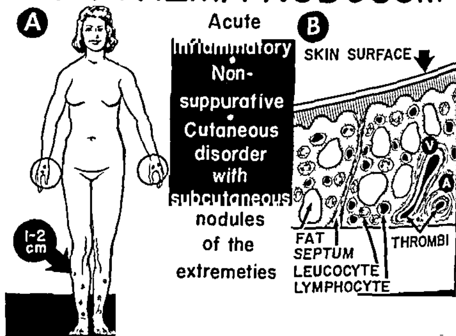


Figure 336. Clinical and pathologic findings in patients with erythema nodosum. (V) is a vein and (A) is an artery.

INFECTIOUS ARTERITIS

Arteritis has been described with syphilis, tuberculosis, pneumonia, typhoid fever, typhus fever and other infections. Arteritis may lead to aneurysms, as in the case of syphilis or to inflammatory thickening of the vessel wall with or without thrombosis of the vessel. The diagnosis of infectious arteritis is made by recognizing the underlying infectious disease with the demonstration of arterial disease clinically, by laboratory methods, or by biopsy. Arteritis may be associated with the Waterhouse-Friderichsen syndrome.

Waterhouse-Friderichsen Syndrome: The syndrome is defined as a fulminating septicemia due to an infectious agent with sudden onset, febrile reactions, purpuric extravasations, evidence of vascular damage especially in the adrenals and with circulatory collapse (figure 337).

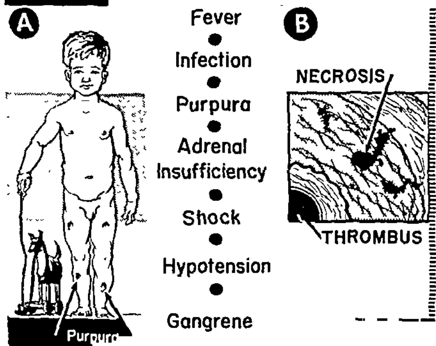


Figure 337. Clinical and pathologic findings in patients with infectious arteritis (Waterhouse-Friderichsen Syndrome).

Etiology: Usually a meningococcic infection with adrenal insufficiency is the cause (35, 36). Other overwhelming infections may produce the syndrome. The hemophilus influenza, pneumococcus and streptococcus may be causative agents as well as the meningococcus.

Age and Sex: Ninety per cent of the cases appear in children under the age of 9 and 70 per cent under the age of two years. Both sexes are affected.

Pathology: There is gross evidence of purpuric extravasation; petechiae and gangrene may be present on the limbs (37). Microscopically there is evidence of capillary destruction with septic arterial thrombosis and arteriolar necrosis. Thrombi may be present in the vessels (36). There is evidence of destruction of the adrenal glands bilaterally.

History and Physical Examination: There is a sudden onset of chills, fever, headaches, general aches and pain, malaise and vomiting. The patient appears ill with petechiae and purpuric extravasations. The blood pressure is low with a rapid pulse and shock. The purpuric spots may become gangrenous (40).

Laboratory Studies: Blood culture often shows meningococci. The organism may be found in petechial areas or spinal fluid. Marked leukocytosis is present.

Course: A downhill course with death is common in untreated cases.

Treatment: Large doses of cortisone (Solu Cortef® intravenously) and adrenal steroids, fluids, penicillin and sulfadiazine are indicated along with specific antibiotic therapy (37, 38, 39).

ALLERGIC ANGIITIS

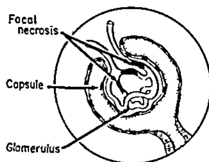
This is a vascular reaction to an antigen and exists in acute (hypersensitive angiitis) and chronic (allergic granulomatous) forms. Both of these diseases are the result of an antigen, antibody reaction. Males and females of all ages are affected (figure 338).

HYPERSENSITIVE ANGIITIS: This is an acute reaction to an allergen which results in an allergic reaction which may terminate fatally in a few days or weeks. The antigen may be horse serum (47), egg white, sulfa drugs (41) or other agents (42, 43, 44, 45). The lungs and spleen are commonly involved in the reaction. Focal necrotizing glomerulonephritis may occur and terminate the disease.

ALLERGIC GRANULOMATOUS ANGIITIS: This is characterized by a history of asthma or other allergies (45, 46). Vascular reactions

occur in larger blood vessels than in hypersensitive angiitis. Commonly the coronary arteries are involved. Giant cell granulomatous reactions are present around these vessels. Urticarial lesions may occur in the skin. Microscopically hemorrhages, urticarial edema and hyperemia are present. The granulomas are in various stages of development. Microscopically venules or arterioles may be surrounded by clusters of eosinophils and neutrophilic leukocytes and the vessels may show fibrinoid degeneration.

ALLERGIC ANGIITIS



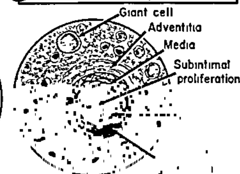


Figure 338. Clinical and pathologic findings in patients with allergic angiitis

Differential Diagnosis: Allergic angiitis must be differentiated from periarteritis nodosa, temporal arteritis and rheumatic angiitis.

Periarteritis Nodosa: This is associated with hypertension and arterial aneurysms. The lungs, spleen, pancreas, kidneys, gastrointestinal tract and veins are involved The prognosis if untreated is poor.

Temporal Arteritis: The temporal arteries are involved. Cellulitis of adjacent tissues occurs The prognosis is relatively good.

Rheumatic Angiitis: This is associated with severe rheumatic carditis. The arteries of the lungs and heart are involved.

Treatment: Large doses of ACTH, prednisone, epinephrine, ephedrine and antihistamines should be tried. Offending antigens should be removed.

NONSPECIFIC ARTERITIS

This includes vascular lesions produced by a variety of agents and diseases which do not fit the groups already described. The vascular skin lesions of Hodgkin's disease are an example.

PULSELESS DISEASE

Takayasu's Disease, Branchial Arteritis

This is a disease of the branches of the thoracic aorta characterized by progressive occlusion of the large vessels in the region of the aortic arch.

History: It was described by Takayasu in 1908 (48) and was named "pulseless disease" by K. Shimizu who suggested the diagnostic triad of absent pulse, eye changes and carotid sinus sensitivity (49). The name "branchial arteritis" has been suggested also (50). Twelve autopsied cases have been reported in the literature.

Sex and Age: Women between the ages of 18 and 43 are commonly affected.

Etiology: It may be that the etiology varies in different cases (54). Usually the disease is inflammatory in nature but the etiology is unknown in many cases.

Pathology (figure 339). An inflammatory proliferative and stenosing process is present in the large branches of the aorta. The early lesions consist of an acute neutrophilic periarteritis, which progresses to panarteritis and causes arterial thrombosis. Later stages are characterized by fibroblastic hypertrophy of adventitia and chronic inflammatory change (50).

History and Physical Examination: Pulsations are absent in one or both arms or in the carotid or temporal arteries (53). Pain in the arm with ischemia of the arms and hands may be present (51). Blurring of vision or blindness, retinal defects and cataracts are

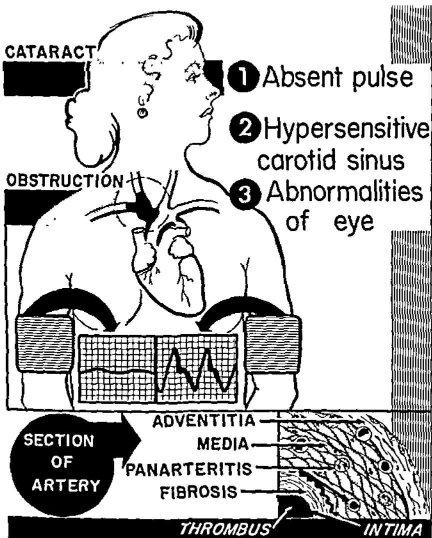


Figure 339 Clinical and pathologic findings in patients with pulseless disease.

common. Hypersensitivity of the carotid sinus with syncopal attacks which are precipitated by turning the head from side to side or from suddenly rising from a supine to a sitting position is common. Coronary insufficiency may be present (52). Deafness also has been reported.

Differential Diagnosis: Takayasu's disease is an inflammatory arteritis distinct from other diseases of the aortic arch (52). The differential diagnosis includes: syphilitic aortitis with or without aneurysms; atherosclerosis with or without aneurysms; congenital anomalies of the branches of the aorta; chronic dissection of the aorta; thrombophilia; Buerger's disease; polyarteritis nodosa temporal arteritis involving the large branches of the aorta; extravascular upper mediastinal tumor; thoracic outlet syndromes with or without cervical rib; neurogenic pulse changes associated with brain damage and embolus to a distal portion of the vascular system with vasospasm.

Prognosis: Pulseless disease is chronic and progressive with remissions. It is a serious disease because most patients die before the age of forty from cerebral ischemia or coronary insufficiency.

Treatment: This is generally unsatisfactory. Thrombectomy, sympathetic denervation of the carotid sinus, or grafting of the carotid artery have not been successful. Removal of the carotid sinus may prevent syncope but does not arrest the course of the arteritis. Antibiotics, steroids and anticoagulants have not had adequate trial but could be used.

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CHAPTER 32

Collagen Diseases

The collagen diseases which will be discussed here are disseminated lupus erythematosus, periarteritis nodosa, scleroderma and dermatomyositis Normal collagen is an amorphous ground substance which occurs in the intercellular spaces. It can be recognized by its deep staining with toluidine blue. Within the amorphous substance often there are collagenous fibers which occur in bundles and probably arise from fibroblasts. In the collagen diseases there is swelling of the intercellular ground substance which becomes granular and stains pink with eosin The collagen fibers may fragment and degenerate producing fibrinoid degeneration.

DISSEMINATED LUPUS ERYTHEMATOSUS

This disease may be defined as a symptom complex with characteristic skin eruptions, constitutional symptoms and visceral manifestations.

Sex and Age: About 80 per cent of the patients are females and the age is generally from twenty to forty years, however, cases have been reported from ten to eighty years of age

Etiology: Inciting agents have been sulfa and other drugs, exposure to sunlight, x-ray, ultraviolet radiation, infection and trauma; however the cause of the disease usually is unknown.

Pathology (figure 340): Lesions of the skin occur in a butterfly distribution over the nose and cheeks and show local atrophy of the skin Diffuse exudative manifestations, for example effusion into the pericardial sac, pleural cavities, abdomen and synovial spaces may occur (1, 2). Non-bacterial endocardial lesions may be present on the heart valves or on the mural endocardium (Libman-Sacks syndrome) (13). Enlargement of the liver and spleen and diffuse lymphadenopathy are common. Hemorrhage and

degeneration of focal areas in the central nervous system, focal necrosis of the liver, inflammatory changes in the muscle and vascular changes deep in the skin are common. Microscopic abnormalities of connective tissue are present which are proliferative, degenerative and inflammatory. Fibrinoid degeneration of

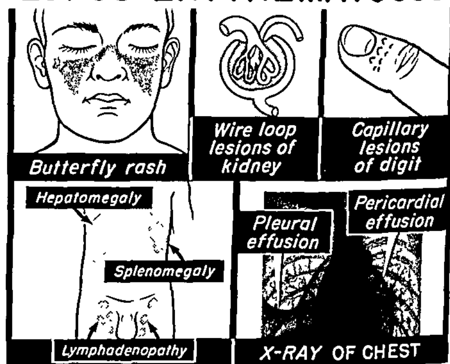


Figure 340 Clinical and pathologic findings in patients with disseminated lupus erythematosus.

the tissues is present in the blood vessels, especially in the heart, lungs, kidneys and spleen. The capillaries, arterioles and venules are involved often in the degenerative process with thrombus formation. Extravasation of serum and cells in the vessel wall and necrosis are observed in the kidney, with thickening of the capillary walls which stain deeply eosinophilic (wire loop lesions)

(13). Concentric rings of collagen about the small arteries of the spleen occur. The myocardial changes include primary changes in the muscle cells or changes secondary to obstruction of the coronary arteries. Vegetations on the heart valves from the valve cusp extending down the chordae tendenae to the mural endocardium occur. Hematoxylin staining bodies have been reported in the cardiac lesions as well as elsewhere in the body. The fibroblasts and leukocytes may contain inclusions similar to the L E cell inclusions described by Haserick (4) and Hargrave (5). These bodies are thought to arise from an alteration in the nuclei of the cells.

History and Physical Examination: The history may be that of general decline, fever, weight loss, rash, abdominal pain, joint pains, arthralgia, dyspnea, orthopnea, precordial pain, palpitation and pleurisy. Nausea, vomiting, anorexia and diarrhea suggest gastrointestinal involvement (12, 14). Localized or generalized lymphadenopathy is present in a significant percentage of patients; the cervical and axillary regions are the usual sites involved. Cerebral involvement is suggested by headache, delirium, irritability, tremor and coma. Visual disturbances occur from retinal degeneration and often there is papilledema and retinal arterial occlusion. The skin lesions when well developed consist of raised indurations with silvery scales. Central atrophy of the lesion may appear later and pigmentation sometimes follows healing. Erythematous changes about the nail bed and on the thenar and hypothenar eminences are common. Small bullous lesions, purpuric spots, urticaria, subcutaneous nodules, vitiligo or ulceration of the buccal mucosa may occur. The Raynaud's phenomenon and alopecia are not uncommon. The butterfly shaped rash on the face and atrophy of the skin is characteristic of the late stage of the disease. Fever which is low grade, high or spiking of the "picket fence" type may be present along with tachycardia. The tachycardia is often out of proportion to the fever. The joints often are red, tender and show evidence of inflammation. Fusiform swelling of the proximal interphalangeal joints may be present. There is a marked degree of muscle tenderness, often of the calves. Pericardial friction rub or cardiac murmurs associated with pleural effusion or adhesive pericarditis may occur. The

development of an apical diastolic murmur in the presence of typical L.E. cells suggests the Libman-Sacks syndrome (13).

Laboratory Findings: The urine often shows albumin, casts and red cells. A normocytic anemia is common and a mild leukopenia (less than 6000 cells) is the rule. A hemolytic anemia with a positive Coombs test represents a serious complication. Thrombocytopenia is common. The plasma proteins are abnormal. The serum albumin is depressed and the serum globulin increased. Usually the concentration of albumin is less than 4 grams per cent and the concentration of globulin above 3 grams and may be as high as 6 or 7 grams per cent. The sedimentation rate is usually rapid Positive flocculation tests and elevated thymol turbidity tests are common. A false positive or anticomplimentary fixation test for syphilis is present if the protein constituents are altered. Spinal fluid protein may be increased.

Electrophoretic Studies: These have demonstrated that the blood of patients with lupus erythematous may contain four abnormal proteins in the gamma globulin fraction (6). 1) One is the L.E factor which is responsible for the L.E cell phenomenon. 2) Another gives rise to a false positive serologic reaction for syphilis. The biologic false positive reaction of disseminated lupus may be differentiated from syphilis by employing the Treponema pallidum immobilization test (TPIT) which is positive only in the presence of syphilis (7, 8). 3) Another gamma fraction acts as an anticoagulant. This may be the cause of the bleeding into the skin and mucous membranes which is common with this disease. 4) The last fraction is responsible for a positive direct anti-globulin test which occurs in some of the patients. Other manifestations of disturbed blood proteins are positive cephalin cholesterol flocculation and thymol turbidity tests which are found in most patients

The L.E. Phenomenon (figure 341). This involves the degeneration of leukocytes (5) The nuclei become homogeneous and chromatin disappears. The cellular membranes rupture and amorphous nuclear material is released. Extruded nuclear masses are surrounded b[illegible] forming classical rosettes [illegible] g, they are less specific th[illegible] eutrophilic

granulocyte containing one or more inclusion bodies composed of neutrophilic nuclear material Only a thin rim of cytoplasm is visible The nucleus is compressed against the cell membrane by a large homogeneous, globular inclusion body which is larger than

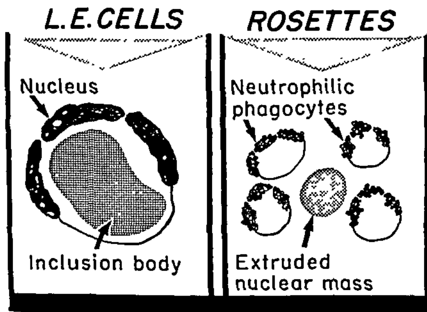


Figure 341. Blood picture in patients with disseminated lupus erythematosus

the leukocyte nucleus The inclusion body is structureless and hyaline in appearance.

Tests for L E. Factor: These tests may be carried out by adding suspected L.E. plasma to human marrow, dog bone marrow or to peripheral human cells. The L.E. factor which is tested for may

be defined as that substance in plasma or serum (usually from patients with systemic lupus erythematosus) which induces leukocytic clumping and/or L.E. cell formation.

Mechanism of the L.E. Phenomenon: There are three important factors necessary for producing this phenomenon: 1) the L.E. factor in the gamma globulin of the patient which causes lysis of cell nuclei as shown by swelling and decreased staining reaction of the chromatin of the affected cells; 2) appropriate nuclear material with which the L.E. factor can react which comes from the polymorphonuclear leukocytes and is obtained from the peripheral blood of a donor, and 3) phagocytic cells which engulf the lysed mass. Usually neutrophilic polymorphonuclear leukocytes become the phagocytic cells; however, eosinophilic polymorphonuclear leukocytes may function in a similar manner. The phagocytic leukocytes may come from the peripheral blood of a normal subject or from the patient with systemic lupus.

Important Technical Factors: Time and coagulation are important secondary factors in the production of the L.E. phenomenon. 1) Time: The L.E. cell phenomenon is an in vitro manifestation and apparently does not occur frequently in vivo. About twenty minutes is a minimal time necessary to bring about the L.E. cell phenomenon. In some cases as long as two hours may be required before the phenomenon occurs. 2) Coagulation: The production of L.E. cells is accentuated by coagulation and depressed by anticoagulants; therefore, the test is best carried out in the absence of anticoagulants (10).

TECHNIQUES: Two techniques will be described (5, 9, 10, 11, 12). One employs patient serum plus donor cells and the other employs only patient blood.

1) Patient Serum Plus Donor Cells: a) Allow 10 cc of the patient's blood to coagulate and pipette off the serum for use as the menstruum. b) Mix 10 cc of blood from a healthy donor with a small amount of heparin to prevent coagulation and centrifuge at 1800 to 2000 rpm for about five minutes. (This blood may be defibrinated to avoid use of an anticoagulant.) c) Pipette off the buffy coat of leukocytes, mix with the patient's serum and allow this mixture to stand at room temperature for 20 to 30 minutes. d) Centrifuge the mixture as before and again pipette off the

cellular layer. e) If necessary, centrifuge the resulting cellular concentrate again in a Wintrobe hematocrit tube. f) Make smears on chemically clean glass slides or cover slips, as is done for blood or bone marrow preparations and stain by the usual technique. g) Examine the preparation under an oil immersion objective.

2) *Patient's Blood Only.* This technique is preferred generally as a donor's blood does not have to be employed. Great caution must be employed, however, in distinguishing nuclei damaged by the mechanics of the procedure from nuclei lysed by the L.E. factor as leukocytic nuclei which are damaged by the technique may be phagocytized (tart cells) and resemble L.E. cells. Procedure: 1) Put 2 to 4 cc of venous blood from the patient into a chemically clean test tube and allow the blood to coagulate at room temperature for two hours. 2) Loosen the clot and centrifuge for five minutes at 1500 rpm. 3) Discard the pipetted serum. 4) Break up or repeatedly puncture the clot with a glass rod or wooden applicator stick. 5) Fish out and discard the clot. 6) Centrifuge the tube as before and make smears of the sediment for staining.

Interpretation: Free masses of lysed nuclear material with or without neutrophilic polymorphonuclear leukocytes clustered about them are suggestive of the L.E cell phenomenon. A positive diagnosis should not be made without identification of a true L E. cell. Distinction between the damaged, engulfed leukocytic nuclei seen in tart cells and L E cells is essential if false positive reports are to be avoided

Treatment: Symptomatic measures include good nutrition, adequate rest, salicylates for arthralgia, alcohol rubs for fever and treatment of secondary infections Sulfonamides probably are contraindicated and sunshine is to be avoided. The offending pathogen should be identified if possible. Antibiotics should be discontinued as soon as possible as they may become antigenic. Transfusions are employed if anemia is severe. The treatment of heart failure is traditional.

Steroid Therapy: Steroids are employed in patients in whom simpler methods have failed (15). The amount of steroid given varies with the severity of the illness. The following treatment schedule is proposed: ACTH gel, 20 to 40 mg daily in a single

intramuscular injection for three weeks, followed by prednisone orally, 20 to 40 mg daily for three weeks after which 25 to 50 per cent of the initial dose is given daily. If relapse occurs, the dose is increased, otherwise the dosage is continually lowered. It is necessary to produce a Cushing's syndrome in certain cases to control symptoms. Occasionally the agent should be stopped but must be resumed if relapse occurs. A low sodium, high potassium diet is desirable during the steroid therapy. When cardiac failure is present and water retention is undesirable, cortisone should not be employed and prednisone is preferred. Prednisone generally is preferred to prednisolone as the former probably has greater anti-inflammatory properties and may not cause as much sodium and water retention and potassium excretion. Both of these agents produce peptic ulceration and diabetes with about equal incidence. ACTH probably is less satisfactory than prednisone for long term therapy as it must be given parenterally. For long term therapy anticholinergic drugs (Probanthine®), antacids and frequent feedings are desirable to prevent peptic ulceration In a crisis, larger doses of steroids may be necessary. As much as 4000 mg of cortisone per day for six weeks have been given in some cases; however a Cushingoid appearance (moon face) is produced and remains until the dose is lowered.

NITROGEN MUSTARD: This can be given intravenously as methyl-bis(beta-chloroethyl) amine hydrochloride and orally as triethylene melamine (TEM). The latter is probably too toxic to use in most cases of systemic lupus. The dose is 2.5 mg orally twice weekly for 4 weeks. The intravenous dose for an adult is about 20 mg after sedation in a single dose given weekly if necessary. The drug is indicated in patients who have renal disease with nephrosis and who are edematous. After a few days or weeks a marked diuresis occurs. Acute systemic lupus without renal damage generally is not benefited (16, 17).

ANTIMALARIAL AGENTS: Chloroquin (Aralen®), amodiaquin (Camoquin®) and quinine are beneficial and exert a non-specific anti-inflammatory effect. They are especially effective in the cutaneous lesions of discoid and systemic lupus. The dose should be increased to the point of maximum clinical effectiveness or to tolerance (15, 18).

Chloroquin (Aralen®): This may produce such side effects as toxic dermatitis, yellow discoloration of the skin or cyanosis The usual maintenance dose is 400 mg per day. As little as 100 mg daily may be employed The suggested starting dose is 100 mg three times daily after meals. If no improvement occurs within a week the dose can be increased to 600 mg a day. Dermatitis, leukopenia and convulsions with muscle weakness may occur. The agent is primarily effective against the cutaneous lesion of systemic and discoid lupus.

Amodiaquin (Camoquin®): The initial dose is 800 mg daily until fever is reduced. The side effects are similar to chloroquin.

Course: Relapses and remissions may occur. It is probable that remissions are longer and life extended with the use of steroids and other therapies. There is objective improvement in cutaneous lesions and joint abnormalities and a reduction in fever; however other manifestations of the disease remain essentially unchanged

Prognosis: The prognosis varies considerably with different patients depending upon the organs involved; however the disease usually is a fatal one. About 10 per cent of the patients die within a year. The cause of death usually is renal failure, arteritis or phlebitis of the central nervous system, or secondary infection.

PERIARTERITIS NODOSA

POLYARTERITIS NODOSA, PANARTERITIS NODOSA, KUSSMAUL-MAIER DISEASE

This may be defined as an inflammatory vascular disease which involves medium sized and small vessels of the peripheral vascular system or viscera (19, 20).

Age, Sex and Race: Most cases occur between the ages of twenty and fifty; however cases have been reported in infancy and in the elderly patient. The disease is more common in males than females (ratio of 3:1) (21). Caucasians, Negroes, Japanese races are affected primarily.

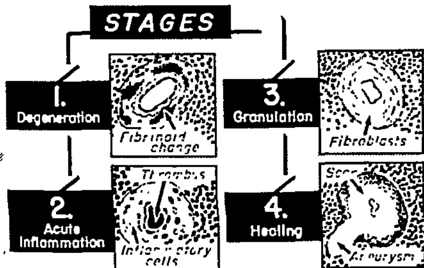
Etiology: This is not well established; however, sensitivity to various antigens is an important feature (22, 23). Selye states that the disease can be reproduced in experimental animals by stress and mineral corticoids (24). Gruber suggested that systemic hyperergic reactions of previously sensitized blood vessels by agents such as bacteria and toxins was a cause. This was based

on the observation that repeated injections of horse serum or foreign proteins in animals produced a reaction similar to periarteritis nodosa (25). Clinically the disease has been found in patients who have received sulfonamides, Dilantin, thiouracil, heavy metals, stilbamidine, hydantoin, proplythiouracil, and in patients with trichinella infection, tropical eosinophilia, Felty's syndrome and Cogan's syndrome (26, 27, 28).

Pathology (figure 342): Small and medium sized visceral and peripheral vessels are involved, such as the vessels of the central nervous system, heart, liver, spleen, lungs, eyes and mesentery (29, 30, 31). Four stages of the disease may be seen (32): Stage I, the stage of necrosis, shows coagulation necrosis of the media of vessels and edema of this layer with a fibrous exudate involving the internal elastic membrane. Stage 2, that of acute inflammation, shows often local thrombosis with infiltration of the media and adventitia by lymphocytes, eosinophils and polymorphonuclear neutrophils with further destruction of the internal elastic membrane. Stage 3, the stage of granulation, shows intimal proliferation often with occlusion of the vessel. Stage 4, that of healing, shows fibrous scar tissue formation, often with marked obliteration of the lumen, or aneurysms.

History and Physical Examination: The onset may be acute or subacute and the disease may follow some other illness. The complaint is frequently that of pain involving the extremities (37) or abdomen or of soreness in the muscles or joints, especially during exercise. Fever usually is present and runs an irregular course. Weight loss, hypertension, icterus, muscular weakness and lassitude may occur The physical examination may show nodules along arteries which are found in about 25 per cent of patients (33). Initially the arteries are tender and the overlying skin erythematous. The nodules are transient and vary from a few millimeters to a centimeter in size and are more common in the upper than in the lower limbs. The pulsations of the diseased artery segments may be diminished because of the thickened wall. Other skin lesions are petechiae, ecchymosis, purpura and urticaria. Abdominal tenderness is not unusual and is common in patients who have lesions of the ileum and jejunum. Hepatomegaly may be present, especially if an hepatic infarct has

PERIARTERITIS NODOSA



MULTIPLE SYSTEM DISEASE

- Nephritis
- Hypertension
- Gastrointestinal symptoms
- Hepatomegaly
- Cardiac failure or pericarditis
- Myositis and neuritis
- Fever
- Weakness
- Postive biopsy

Figure 342 Clinical and pathologic findings in patients with periarteritis nodosa

occurred (34). The central or peripheral nervous system may be involved and ischemic neuritis may be present. The peroneal, tibial and median nerves often are involved. Renal involvement is common and may be a cause for the hypertension (35).

Laboratory Findings: The white count is usually elevated. Eosinophilia may be present and the sedimentation rate is increased. Microcytic hypochromic anemia may occur. Albuminuria is common. Biopsy of muscle is an important diagnostic aid and should be repeated if necessary to establish the diagnosis. Obstruction of individual arteries, for example the radial artery distal to its point of palpability, may be demonstrated plethysmographically.

Differential Diagnosis: Periarteritis nodosa is to be differentiated from subacute bacterial endocarditis, erythema nodosum, neurofibromatosis, abdominal types of Hodgkin's disease, purpura of various causes, neuritis of various etiologies, trichinosis, peptic ulcer, appendicitis, ulcerative enteritis, mesenteric thrombosis, hemorrhagic pancreatitis, tuberculosis, carcinoma, mesenteric adenitis and other disease states. A skin test for trichinosis using an antigen of 1:10,000 is helpful in ruling out this disease. Blood platelets, coagulation times, prothrombin times and other blood tests should be carried out to rule out diseases of the blood. Blood cultures assist in ruling out subacute bacterial endocarditis.

Prognosis: This varies with the severity of the disease. Death may occur in two or three weeks or the patient may recover. The condition is sometimes recurrent. The life expectancy is shortened in most patients.

Treatment: The sensitizing factor should be removed (stop sulfa, etc.). Adrenal steroid hormones should be employed as described for disseminated lupus erythematosus. These agents often produce a prompt drop in fever with temporary clinical improvement; however relapses occur frequently when the drug is discontinued (36). Healing of local lesions sometimes takes place; however in the course of healing fibrous obliteration of the vessel occurs which results in infarcts. Para-aminobenzoic acid may be effective. Vasodilators should be employed where there is evidence of functional vasoconstriction. These include Priscoline®, Roniacol®, alcohol and body heating.

DIFFUSE SCLERODERMA

Progressive Systemic Sclerosis

This may be defined as a systemic disorder of unknown etiology which involves connective tissue of the skin and subcutaneous muscles, fascia and tendons, with involvement of internal organs (38, 39).

Types: Scleroderma may be local or diffuse. Morphea represents a local sclerodermatous lesion involving often a small portion of an arm or leg. This remains localized and visceral involvement does not occur. Acrosclerosis is also a local type which involves only the distal part of the limbs (41). Sclerodactylia is a local type which involves only the digits and is often secondary to long-standing Raynaud's disease and is not related to diffuse scleroderma. Generalized diffuse scleroderma which is discussed here is a systemic disease which involves skin and many organs of the body.

Sex and Age: The disease is twice as frequent in females as in males and occurs commonly between the fourth and fifth decades (40). It is unusual before the age of six. The etiology is unknown.

Pathology (figure 343): The small blood vessels of the viscera, skin and subcutaneous tissues show changes in the adventitia, media and intima. Intimal thickening occurs which consists of an acellular fibrinoid material. Necrosis and fibrous replacement of the media and cellular infiltration of the entire vessel wall occurs. Thrombosis is common. The radial artery may show intimal proliferation; however, the larger arteries are essentially normal. The digital arteries often are almost completely obliterated by intimal proliferation. The epidermis of the skin is thin with a few flattened or broadened papillae. The dermis consists of compact subcutaneous fat. The elastic fibers are decreased and fragmented. In the deeper areas, the collagen tissue is hyalinized and calcareous degeneration is present (41). In certain cases thickening of the epidermis may occur (42). The heart often shows replacement of the myocardium by dense collagenous tissue which is not related to coronary artery disease. In addition, there is an increased amount of connective tissue between

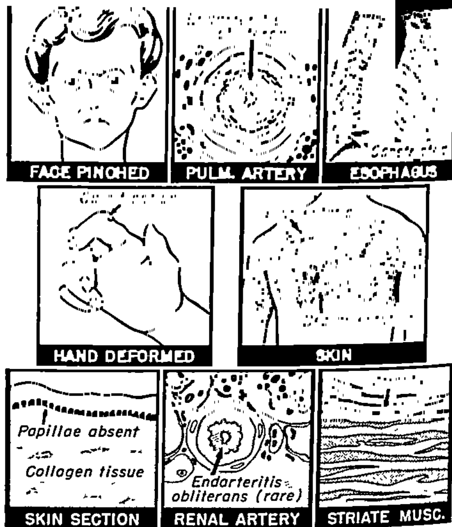


Figure 343. Clinical and pathologic findings in patients with scleroderma.

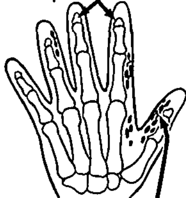
the muscle cells (43). The esophagus may show ulcers and constriction due to fibrosis. The colon and intestinal tract may show atrophy of most tissues (44, 45). The lungs show bronchopneumonia with thickening of the alveolar septa with interstitial fibrosis (46). The kidneys show thickening of Bowman's capsule

with areas of cortical necrosis and hyalinization of glomeruli and capillary loops. Hypertrophy of the intima of the renal arteries is common and infarcts of the kidneys may be present with coagulation necrosis (43, 47).

History and Physical Examination: Typically there are numerous complaints as many different organs are involved. Stiffening of the skin of the hands and body with pigmentation and depigmentation is a common complaint Dysphagia and dyspepsia occur when the gastrointestinal system is involved Asthenia and weight loss may be present when swallowing is difficult because of involvement of the lining of the esophagus Dyspnoea, orthopnea and cyanosis may be present when degeneration of the heart has taken place. In the early stages of the disease the skin is edematous. Later the skin becomes firm, non-distensible and wax-like and the joints become stiff. Calcification of the tissues and absorption of the terminal phalanges with severe deformity of the hands occur. Vasomotor disturbances such as hyperhidrosis, pallor, coldness or the Raynaud phenomenon may be noted. Atrophy of the fingertips with pointed fingers result from loss of subcutaneous fat. The nails may be deformed, shortened or cracked. Ulcers of the skin are common and subcutaneous deposits of calcium may be felt under the skin, especially in areas which are subjected to pressure, such as the tips and volar surfaces of the fingers, elbows and the skin anterior to the tibia. The face in advanced cases is mask-like, devoid of wrinkles and furrows with thinning and puckering of the lips. There is eversion of the lower lip and the mouth cannot be opened fully. The nose is pointed because of loss of subcutaneous tissue. Crepitant or subcrepitant rales may be heard in the chest and are often secondary to bronchopneumonia.

Laboratory Findings (figure 344)· Hand prints showing the span are useful for revealing the results of treatment X-ray of the bones of the hands may show subcutaneous calcification and absorption of bone. Gastro-intestinal x-ray series may show peptic ulcer, constriction of the esophagus, spasm of the cardia or hiatus hernia which results from shortening of the esophagus. There may be lack of peristalsis and stasis in the large and small bowel with narrowing of the lumen with rigidity or sacculation seen by











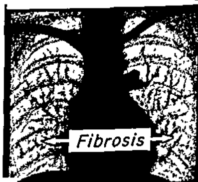


Figure 344 Laboratory findings in patients with scleroderma.

x-rays. The electrocardiogram shows T wave changes which are non-specific. The heart may be enlarged. X-ray of the chest may show fibrosis of the lungs and bronchiectasis may be present. Right heart failure may occur if the pulmonary vessels are involved and pulmonary hypertension results. The blood count is not unusual. The urine test may show albumin when the kidney is involved. Organic vascular disease of the digits is demonstrated

by failure of the skin temperature to reach normal values after a posterior tibial nerve block. The digital plethysmographic method of estimating blood flow is not valid in this disease because the tissues of the digits are rigid.

Treatment: Massage of the part with lanolin, exercise and protection of the fingers from ulceration and avoidance of exposure to cold are of value. Prednisone or prednisolone, cortisone or ACTH results in slight improvement in some cases; however the results generally are discouraging (48).

Relaxin (Releasin®): It has been reported that relaxin (Releasin®) combined with an estrogen loosens collagenous tissue. This is based on the observation that relaxin produces softening of the cartilage of the symphasis pubis of the ginuea pig which allows delivery of the young (see chapter on treatment). This form of treatment, although unproved, may be tried for two months at recommended dosage levels and continued with fewer injections if the results appear encouraging.

Iontophoresis: Mecholyl and other substances have been employed with this method with slight success (38).

Sympathectomy: This is of limited value. It may be employed in the early stages if an increased vasomotor tone can be demonstrated. It does not stop the development of lesions of the organs, heart, lungs, esophagus, etc (49).

Vasodilators: Priscoline®, Roniacol® and Dibenzyline® and alcohol are indicated but the results are poor.

Prognosis: The disease may progress either rapidly or slowly. When vital organs are involved the disease may be fatal.

DERMATOMYOSITIS

This is a collagen disease of unknown etiology which is characterized by nonsuppurative inflammation and degeneration of voluntary muscles, often with changes in the skin (figure 345).

Age and Sex: The disease affects children and adults. Both sexes are affected.

Etiology: This is unknown, however an association with malignant neoplasm such as adenocarcinoma of the stomach and clear cell adenocarcinoma of the kidney has been noted (50).

Pathology: In the acute stage there is inflammation of the muscle bundles with loss of transverse striations and separation of the myofibrils. There may be a round cell infiltration around the smaller vessels In the chronic stage there is widespread

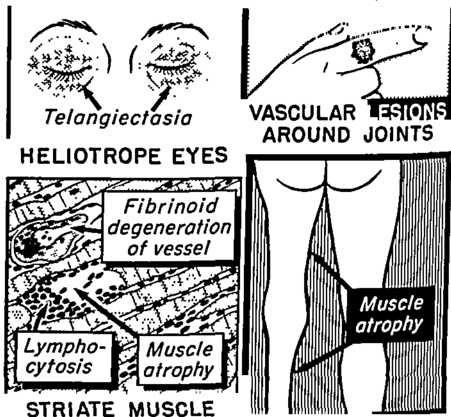


Figure 345 Clinical and pathologic findings in patients with dermatomyositis.

muscle destruction. Usually there is no evidence of endothelial proliferation or obliteration of arteries.

History and Physical Examination: In the early stages there is weakness, weight loss, nausea, fever and muscle pains, often with edema of tissues, tenderness and dermatitis. The Raynaud's

phenomenon may be present. Difficulty in swallowing, double vision, weakness of the tongue and sphincters may be present. In the early stage the muscles may be swollen, tender and have a doughy consistency. In the late stage they are atrophic and painless. There is a tendency for the muscle involvement to be bilateral. The oral temperature may be elevated at times. Skin lesions may or may not be present. When present they are often non-specific showing only erythema and edema. Edema and erythema around the eyes may be present producing the "heliotrope" eyelids of this disease. Close observation shows that the discoloration is due to the presence of numerous telangiectases. When present for long periods of time, pigmentation may occur around these vessels (51). Telangiectasia is present often around the small joints of the hands. Calcification of the skin and muscles may occur. Calcified areas are most common around the joints.

Laboratory Work: The sedimentation rate is usually elevated and there is a mild anemia. Albuminuria and an increased urinary creatinine occur in the more diffuse cases.

Diagnosis: This can be established by muscle biopsy.

Differential Diagnosis: The disease is to be differentiated from disseminated lupus erythematosus which shows the L.E. phenomenon and abnormalities of the plasma proteins and scleroderma which can be differentiated by skin and muscle biopsies (52).

Treatment: A general upbuilding regimen is employed. Testosterone or one of its derivatives, such as Nilevar® may be employed for its nitrogen retaining power. Prednisone, prednisolone, ACTH and cortisone have provided temporary improvement in selected cases (53) Relaxin may be tried (see chapter 50).

Prognosis: Remissions and relapses are frequent: About half of the patients with small muscle groups involved show improvement or very little progression; however death may occur in a few months from respiratory paralysis or pneumonia (54).

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PERIARTERITIS NODOSA

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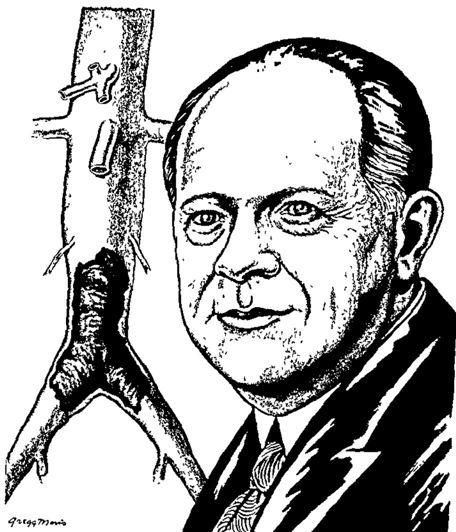


Figure 346 Rene Leriche, 1879 to 1955. He was one of the early surgeons to submit surgery to experimental control. He was the first to perform a stellectomy and from this grew the technique of sympathetic ganglionectomy. He recognized the syndrome associated with chronic progressive obliteration of the bifurcation of the abdominal aorta which is now known as the "Leriche Syndrome."

CHAPTER 33

Arterial Thrombosis

ARTERIAL thrombosis is a clotting of blood in the arterial channels. This may be acute or chronic

Age and Sex: This occurs in middle aged adults and elderly individuals and is more frequent in males than in females because of the higher incidence of arteriosclerosis in males than in females.

Etiology: Inflammatory disorders, such as thromboangiitis obliterans, polyarteritis nodosa, mycotic arteritis or infectious diseases; degenerative conditions, such as arteriosclerosis obliterans; trauma; and abnormalities of the blood, such as polycythemia or thrombotic thrombocytopenic purpura, have all been causes (1, 2, 3). Some of the factors which predispose to the formation of thrombi are: 1) alteration of the intima of the vessel wall; 2) an increase in blood fibrinogen, 3) increased blood globulins or viscosity, 4) hemoconcentration; 5) statis, and 6) an increased number or agglutinability of blood platelets.

Acute thrombosis occurs usually secondary to atherosclerosis or the thrombosis follows a peripheral embolus (figure 347). In the latter case the thrombosis propagates distally and proximally from the embolus for varying distances and extends to the first major branch of the thrombosed artery (4).

History and Physical Examination: The symptoms and signs depend upon the acuteness of development of the thrombus (5). When arteriosclerosis precedes thrombosis there is intermittent claudication with the slow development of impairment of nutrition of the muscles, skin, nerves and other tissues and numbness, tingling and paresthesias are common. The peripheral pulses are diminished distal to the obstruction. The part may be cold and demonstrate pallor and dependent rubor. When acute thrombosis occurs, especially when large vessels are occluded, there is

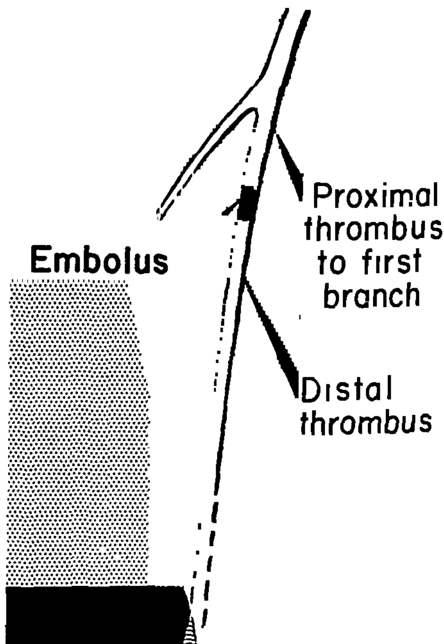


Figure 347. When an arterial thrombosis occurs after an embolus the thrombus often extends distally and proximally to the first major branch of the artery.

the sudden onset of pain, hyperesthesia, anesthesia, motor paralysis and coldness.

Laboratory Findings: The vascular examination shows 1) decreased amplitude of pulsations with rounding of pulse forms and delayed crest time below the site of the obstruction with increased amplitude of pulsations proximal to the obstruction; however, the increase may not be present if arterial spasm occurs (figures 141, 138). The systolic blood pressures likewise are lowered below the site of the obstruction (figure 168). The venous congestion test and skin temperatures are low below the obstruction. A posterior tibial nerve block shows marked increase in pulsations, blood flow and skin temperatures if a good collateral circulation is present. With poor collateral circulation or with disease of digital arteries no significant increase occurs after this procedure.

THROMBOSIS OF THE BIFURCATION OF THE AORTA

Leriche Syndrome

This syndrome was first described in 1940 by Rene Leriche and consists primarily of ischemic pain in the hips and thighs on walking due to obstruction of the abdominal aorta (6).

Etiology: The usual etiology is arteriosclerosis.

Age and Sex: This condition was thought originally to be confined to males, however, recent studies do not show this trend. Middle aged and elderly adults are affected.

History and Physical Examination: The history is that of slow development of intermittent claudication with pain often in the hips, thighs and calves and the inability to maintain an erection because of insufficient blood flow to the corpus cavernosum. The pulses of the lower limbs are small as compared with those of the upper limbs, or they may be absent. When good collateral circulation is present, the tissues of the legs and feet appear essentially normal but if poor circulation is present, trophic changes are present. Elevational pallor and dependent rubor usually are present. Pulsations of the aorta may be felt above the umbilicus. This finding helps to differentiate the Leriche syndrome from coarctation of the thoracic aorta in which aortic pulsations are absent or small in this location.

Laboratory Work: The aortogram shows complete occlusion of the abdominal aorta with or without evidence of collateral circulation (figure 194). The vascular examination shows how pulsations in the legs and low pulsation indexes, low systolic blood pressure in the legs and low systolic blood pressure indexes indicating a deficient circulation in the lower extremities as compared with those of the upper (figure 319). Of particular importance is the demonstration of low pulses in the groins. This is an important finding which rules out superficial femoral artery obstruction as the cause of the deficient circulation in the legs. A good collateral circulation can be demonstrated by the observation that the blood pressure at the ankle does not change after compression of the femoral artery If the disease process is far advanced and the collateral vessels are obliterated, manual compression of the femoral artery results in a marked fall in systolic pressure at the ankle The pulsations of the toes and venous congestion test are low in the lower extremities as compared with the upper (7, 8).

Course: The disease is slowly progressive over a period of years.

Treatment: When the arterial thrombosis is acute, heparin or other anticoagulants are given to prevent further clotting (9). If the thrombus is old a thromboendarterectomy or graft is performed. Resection of the aorta and placement of an arterial homograft have been successful repeatedly for treating chronic thrombosis of the abdominal aorta (10) (figure 320). A thromboendarterectomy may be performed if the involved segment is short and the patient is a good risk surgically (11, 12). Extensive sympathectomy (L1 through L3) produces moderate improvement in patients in whom a posterior tibial nerve block has shown a significant increase in circulation of the digits. Medical vasodilators, alcohol, Priscoline®, Roniacol® and Dibenzyline® are of value if vasodilatation occurs with the posterior tibial nerve block.

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CHAPTER 34

Arterial Embolism

AN EMBOLUS is a blood clot or other foreign material in a vessel, which is located at a site distal from its place of origin. This chapter deals with embolism of the peripheral, visceral (mesenteric) and pulmonary arteries.

Etiology: The common causes of an embolus are atrial fibrillation, rheumatic mitral valve disease, mural thrombi in the atria or ventricles, an arteriosclerotic plaque which may break off from the wall of an artery, trauma to an artery producing a thrombus which may become an embolus, fat or air that is introduced into the venous or arterial systems (1).

PERIPHERAL EMBOLISM

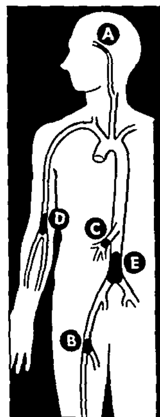
Emboli are common in the aorta, iliac, common femoral, superficial or deep femoral or popliteal arteries (2, 3). They are less common in the arteries of the arms (4) (figure 348).

History and Physical Examination: The patient complains of acute pain at the site of and distal to the embolus. Shock may occur, especially with an embolus to the bifurcation of the aorta. The signs are tenderness at the site of the embolus, muscular weakness and inability of the patient to stand or walk. The part is cold and the limb may at first be white but then mottled. Gangrene may occur if the obstruction occludes a large artery (1, 5).

Laboratory Studies: The volume pulsations of the limb (plethysmographic readings) are decreased below the site of the obstruction. If the artery proximal to the obstruction goes into spasm the plethysmographic readings will be reduced here also until the spasm is released. Digital plethysmograms of the toe show no significant pulsation after a posterior tibial nerve block unless the collateral circulation is adequate. Usually the col-

EMBOLI

PERIPHERAL and VISCERAL



INCIDENCE	%
A Brain	50
B Lower extremities	20
C Viscera	15
D Upper extremities	10
E Aorta	5
TOTAL	100

Figure 348. Common locations for emboli to peripheral arteries and to arteries of the abdominal viscera.

lateral vessels are in spasm at first but later vasorelaxation occurs (6).

Prognosis: Emboli to the aorta carry a poor prognosis. Approximately half of the patients with this lesion die or develop gangrene. Emboli to the popliteal artery also carry a poor prognosis when the embolus obstructs the collateral vessels around

the knee. The prognosis is better with emboli to the iliac and femoral arteries because the collateral circulation generally is better (5, 7).

Treatment: 1) Pain is relieved by morphine or its derivatives, 2) the foot of the bed is lowered to encourage an adequate blood supply; 3) a foot cradle is placed over the legs which are wrapped in cotton wadding to prevent trauma; 4) vasodilators in the form of oral alcohol, Dibenzyline®, Priscoline® and Roniacol® are given; 5) sympathetic spinal or caudal blocks are performed to favor vasodilatation of collateral vessels, 6) anticoagulants in the form of heparin are given intravenously in divided doses every four hours; 7) an embolectomy should be performed promptly after protamine sulfate has been given to stop the heparin effect. When an embolus to the aorta is present embolectomy may be performed through the femoral artery, the embolus being removed from the bifurcation with a corkscrew or suction (8). Post-operatively anticoagulants and sympathetic interruption are helpful and vasodilating drugs are given (9). Ligation of the atrial appendage may be performed in patients with large atria who are fibrillators and in whom clots in the atrial appendage are suspected (10).

VISCERAL ARTERIAL EMBOLISM

Mesenteric Embolism

Emboli to the mesenteric artery may occur from any of the causes mentioned (vide supra). With rheumatic mitral stenosis and insufficiency, thrombosis of the atrial appendage often is the source. Following a coronary occlusion a mural thrombus often forms at the endocardial surface of the left ventricle which becomes an embolus. Less commonly, trauma to the abdomen, or arteriosclerosis, may produce an embolus (figure 348).

History and Physical Examination: The onset of symptoms is sudden. There is acute pain in the abdomen associated with weakness. The intensity of the symptoms varies with the size of the embolus. The patient complains of abdominal distention, constipation or abdominal cramps. Diarrhea or vomiting may be present. A bloody diarrhea may occur. The body temperature is normal unless peritonitis develops. The blood pressure is low

from blood loss or because of reflex sympathetic inhibition of vasomotor activity.

Laboratory Work: X-rays taken in the anteroposterior, lateral and oblique views in the upright and supine positions show distention of the intestinal tract, especially in the upper regions Later, the distention increases with loss of haustrations and fluid levels occur. Very late a "step-ladder" appearance is present.

Pathology: An acute embolus to the mesenteric artery is usually followed by venous stasis distal to the embolus with distal propagation of a blood clot The collateral vessels often are in severe spasm, which further limits the circulation to the intestinal tract. Eventually there is gangrene of the intestinal tract with perforation (11).

Diagnosis: The sudden onset of abdominal pain, distention and intestinal obstruction in a patient with rheumatic heart disease, atrial fibrillation or previous embolism suggests the diagnosis. The disease may be progressive because of distal thrombosis of arteries, capillaries or veins. The abdomen is soft and doughy with persistent tenderness Fever usually is absent early but may occur late.

Treatment: Surgical treatment usually is necessary. If the diagnosis can be made early an embolectomy may be performed. Surgical resection of the gangrenous bowel and its mesentery should be carried out. Exteriorization is indicated when the occlusive process is spotty. Sympathetic interruption either through blocks or sympathectomy may assist in relieving arterial spasm. Injections of procaine into the mesentery may be helpful for this purpose Anticoagulants are used by certain workers to prevent propagation of the clot The vasodilators, alcohol, Priscoline®, Dibenzyline® and Roniacol® may be employed but are of slight value (12, 13).

PULMONARY EMBOLISM

This is an acute obstruction of the pulmonary artery, most commonly caused by a blood clot that usually originates in some distant point in the venous system; however, it may arise from the right atrium or ventricle (14). Commonly emboli are due to 1) thrombi; 2) fat, or 3) air (figure 349).

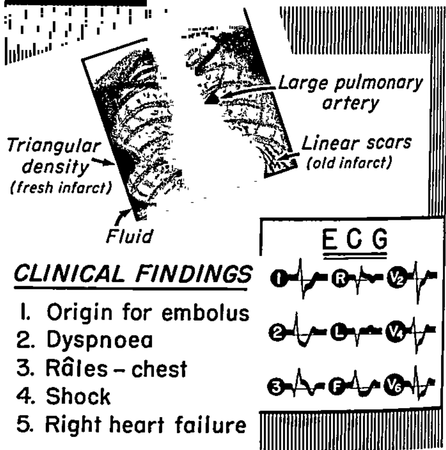


Figure 349. Common findings in patients with pulmonary emboli.

Thrombi

These often are classified as bland and septic. Bland thrombi often originate in the deep veins of the calves or in the iliofemoral veins. A thrombus in any vein, for example the prostatic venous plexus, superficial veins of the limbs with or without varicosities may result in emboli. Phlebothrombosis (thrombosis without signs of inflammation) may result in emboli more frequently than thrombophlebitis (thrombosis with signs of inflammation). Thrombosis of veins and pulmonary emboli occur after periods of

prolonged bed rest, operations, fractures, parturition and with carcinoma, hematologic diseases and cardiac failure. Slowing of the blood stream, injury to the vascular endothelium and alterations of the physical or chemical properties of the blood that promote coagulation are important causative mechanisms. Septic thrombi often originate in the pelvic veins and produce infected emboli to the lungs, which result in pulmonary infarcts and lung abscesses (15, 16, 17).

Age and Sex: The most common age is beyond forty. There is no sex predilection.

Size of Emboli: Emboli vary in size from small clots a few millimeters in diameter which may arise from small veins, for example from the plantar veins of the foot, or they may be as long as 30 cm in length when they form in the large veins (18).

Location of Emboli: Small emboli may lodge in the arterioles and if few in number have very little demonstrable effect. Large emboli may occlude the right or left pulmonary artery or override the bifurcation of the main stem pulmonary artery. The main pulmonary artery may be occluded in such a way that the pulmonary valves are unable to open and pulmonary stenosis results.

Effects on the Heart: The outflow of blood from the right ventricle into the lungs is diminished. There is consequently a rise in right ventricular and venous pressure with decreased filling of the left ventricle and a decreased cardiac output with a fall in arterial pressure. This is one of the causes of shock, which is common during the acute stages of this disease. Also, myocardial ischemia results from the low pressure in the aorta and coronary arteries. However, hypoxia due to decreased pulmonary aeration and reflex vasoconstriction of the coronary arteries produces myocardial ischemia also.

Effects on the Lung: A pulmonary embolus may or may not produce an infarct. Infarcts are most likely to occur when a large embolus is present and when there is pre-existing pulmonary venous stasis, as occurs with congestive heart failure. The collateral circulation through the bronchial arteries may prevent an infarct, especially if the embolus is small.

History and Physical Examination: The major findings are: 1) dyspnea and lung findings; 2) shock, and 3) right heart failure.

The onset is usually sudden with shortness of breath, cyanosis, weakness and chest pain. There may be substernal pressure, hemoptysis, mental confusion and sweating. Shock, hypotension, sweating, cardiac irregularity, angina, mental confusion and syncope are common. When right ventricular failure develops the neck veins become distended An accentuated pulmonary second sound is a sign of pulmonary hypertension. A systolic thrill and murmur over the pulmonary area due to the embolus may be present. Acute congestion of the liver with rapid enlargement may occur. Peripheral edema and the signs of chronic right heart failure are not present early but occur later. Signs due to hypoventilation such as dyspnea, tachycardia and cyanosis are common. Fever is the rule; however this is not necessarily present Signs of consolidation of the infarcted area often develop. There may be a pleural friction rub and local tenderness over pleuritic areas. Signs of effusion may occur. A pulmonary infarct may develop into an abscess, especially if the embolus was a septic one.

Laboratory Work: The electrocardiogram typically shows deep S waves in lead I; with Q waves, elevated S-T segments and inverted T waves in lead III. Lead III resembles a posterior myocardial infarct. Lead I resembles chronic right ventricular strain. Depression of the S-T segments may occur in lead II with a staircase ascent of the S-T segments in this lead. In leads V3 or V4 inverted T waves are common. The electrocardiographic changes are thought to result from myocardial ischemia. Necrosis of the myocardium has been found in some patients with pulmonary infarcts. Leukocytosis is the rule.

X-ray: The pulmonary artery may be dilated. This is especially visible at the left hilum. Obliteration of the costophrenic angle on the affected side may occur because of a pleural effusion. Pulmonary infarcts may be single or multiple, unilateral or bilateral They usually affect the lower lobes of the lung. The densities may be triangular, round or irregular. Atelectasis may occur and rarely a lung abscess develops. Localized fibrosis or linear scars may occur with healing Pulmonary embolism without infarction may cause diminished pulmonary blood flow and a decreased density of the lung tissue.

Diagnosis (figure 349): The diagnosis of a pulmonary embolus involves the recognition of: 1) pulmonary infarction and 2) right ventricular strain. A pulmonary embolus is suggested by the sudden occurrence of chest pain, dyspnea, cyanosis and shock, with the presence of a probable origin for the embolus (for example tender calves or myocardial infarction) Right ventricular strain is revealed by the presence of pulmonary hypertension, congestion of the neck veins, enlargement of the liver and typical electrocardiograms.

Prognosis: Death usually results from the embolus when it involves the main pulmonary artery or one of its major branches Non-fatal emboli may undergo organization and recanalization with recovery followed by chronic heart failure. Small emboli often are not fatal; however recovery may be slow because of pleural effusion or suppuration of the infarct.

Treatment: This involves: 1) prophylaxis, and 2) treatment of the attacks Prevention of venous thrombosis and the avoidance of long periods of bed rest are important Cardiac disease should be treated adequately to prevent right atrial stasis and subsequent thrombosis. Post-operative abdominal distention should be avoided and post-operative patients should be moved frequently Hydration should be adequate and infections controlled Interference with the venous circulation during surgery, such as long periods of immobilization of the legs in abnormal positions, should be prevented. Post-operatively the limbs should be examined daily for tenderness and measurements of the circumference of the calves made. If pain in the chest occurs, a search for thrombophlebitis or phlebothrombosis should be made Anticoagulants in the form of heparin and dicoumarol may be given post-opperatively if the patient is a known thrombus former Ligation of the iliac vein or inferior vena cava may be carried out after one pulmonary embolus to prevent additional emboli from occurring, or this procedure may be performed when thrombophlebitis develops For an acute pulmonary embolus heparin is given immediately to prevent thrombotic extension of the embolus in the lung. Morphine is given for pain and oxygen is given by mask, or if atelactasis is present, by intermittent positive pressure breathing. Atropine 0 6 mg (0 01 grain) intramuscularly may interrupt

vagal reflexes and improve pulmonary arterial collateral circulation. Surgical removal of the embolus has been carried out.

Fat Embolism

This is the obstruction of pulmonary vessels by globules of fat.

Etiology: This occurs usually with blast injuries, during orthopedic procedures or following fractures. The fat enters the veins and travels to the lung and produces arterial obstruction (19). Occasionally the fat passes through the pulmonary capillaries and lodges in the brain.

Symptoms: Characteristically there is an accident, followed by a free interval of six hours to two or three days, after which sudden pain in the chest with shock and pulmonary edema occur (20).

Laboratory Work: X-ray of the chest shows bilateral patchy pneumonic consolidation. Characteristic electrocardiographic changes are unusual but may be present.

Treatment: Oxygen is of value by mask or by intermittent positive pressure breathing (19). Pressor agents, such as levarterenol (Levophed®) should be used if shock is present. Sodium desoxycholine (Decholin®) 10 cc of 20% solution by slow intravenous drip every two hours may emulsify the fat and reduce the size of the emboli.

Air Embolism

An air embolus is a quantity of air that reaches the heart and lungs and interferes with circulation.

Etiology: The embolus may occur during the course of major surgical procedures or during uterine tubal insufflation, urethroscopy, pneumoperitoneum or direct transfusions (21, 22).

Physiology: The presence of air in the right ventricle interferes with the circulation because of its compressibility. The air may obstruct the main pulmonary artery, the pulmonary arterioles or capillaries.

Symptoms: These are weakness, syncope, shortness of breath, cyanosis and collapse.

Laboratory Work: The presence of air in the coronary circulation may produce an abnormal electrocardiogram. The air may be seen in the retinal arteries with the ophthalmoscope.

Treatment: The head down position is advisable to prevent the air from floating into the cerebral vessels. Turning the body onto the left side may trap the air in the right atrial appendage where it does not interfere with the mechanical action of the heart. Inhalation of 100% oxygen has been helpful in animals (23).

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CHAPTER 35

Local Cold Injuries

THESE INCLUDE chilblains, frostbite, trench foot and immersion foot and hand

Physiologic Reactions to Cold: Cold produces vasoconstriction of the arterioles and larger arteries. This results from a local action of the cold on the vessels along with sympathetic vasoconstriction. The presence of cold blood in the brain may be a factor in the production of neurogenic vasoconstriction. Following the vasoconstriction, reactive hyperemia occurs Edema fluid may accumulate in the interstitial spaces which has a protein concentration approximating that of serum The damage done to the tissues may be due to the direct action of cold on the cellular structures, hypoxia and injury to vascular endothelium, or to thrombosis of capillaries The muscles and nerves are sensitive to cold injury as is the skin The amount of tissue damage is dependent upon the intensity of the cold and the duration of exposure.

CHILBLAINS, ERYTHEMA PERNIO, PERNIO

This is a type of tissue irritation which occurs from exposure to cold which results in dermatitis and often ulceration of the skin (figure 350).

Sex and Age: Women are involved more frequently than men probably because their dress is lighter. Any age may be affected.

Etiology: The disease occurs as a result of exposure of the limbs to a cold, wet environment without adequate protection of warm clothes. Patients with an increased vascular responsiveness and those with true cold sensitivity are most susceptible (1).

Pathology: Perivascular infiltration and intimal proliferation with thickening of the arterial walls may be noted. Subcutaneous tissues and skin show a chronic inflammatory reaction with giant cells. Fat necrosis may be present (1, 2).

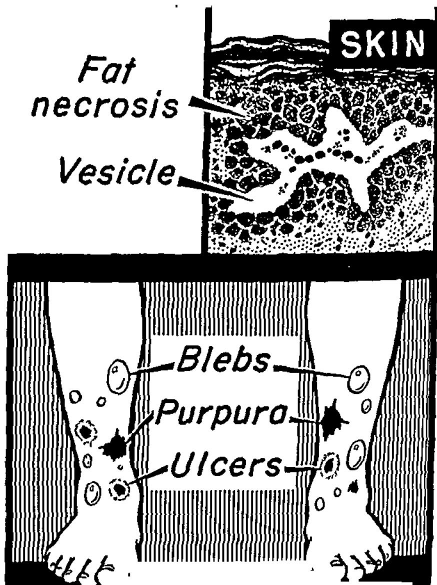


Figure 350. Clinical and pathologic findings in patients with pernio.

History and Physical Examination: There is a history of exposure to cold and often the patient is not aware of injury at the time of exposure. Following exposure, there is burning, reddening and itching in the affected areas. The symptoms are intensified by rapid warming of the previously exposed area. The lesions are generally bilateral and symmetrical and affect the legs, toes and dorsal surfaces of the hands and feet. Blebs filled with clear or bloody fluid may form (3). Purpuric lesions may be present. Superficial ulcers may form and there may be pigmentation. Chronic recurrent skin lesions which develop during cold weather and improve in the summer are suggestive of pernio. Residual scarring and atrophy of the skin and subcutaneous tissue occurs. A dermatitis is seen on the legs and on the dorsal surfaces of the hands and feet. Vesicles, purpuric spots or ulcerative lesions may be present. Pigmented spots may represent old lesions. Excessive sweating of the part may be present.

Laboratory Results: Vascular studies are normal in mild cases but diminished digital blood flow can be demonstrated in advanced cases.

Differential Diagnosis: Pernio can be differentiated from erythema nodosum and erythema induratum because of its seasonal occurrence and because of its production by cold. Raynaud's disease differs in that acute attacks of pain and color changes occur with this disease while the signs are more persistent with pernio.

Treatment: Prophylactic treatment includes dressing warmly and avoiding cold (1). Excessive heat or cold is to be avoided. Secondary infections should be treated with antibiotics locally. Medical vasodilators including Roniacol®, Priscoline® and Dibenzyline® may be of value. Sympathectomy is indicated theoretically but is not an established form of treatment (4).

FROSTBITE

This is an acute local injury produced by exposure to cold.

Sex and Age: All ages and both sexes are susceptible.

Etiology: Frostbite occurs from exposing tissues to extreme cold. The cold is usually at or below freezing. The amount of damage depends upon the intensity of the cold and the duration

of the exposure. The damage is more severe if the circulation is impaired, for example by tight clothing or cramped positions at the time of cooling (5).

Pathology: Early the vessels are constricted and later they become dilated. The walls of the vessels become thickened and edematous The intima is thickened and partially occludes the lumen of the vessel (6). Edema of the cutis is present. Vascular thrombosis occurs with degeneration and necrosis of tissues.

Clinical Types (figure 351): First degree frostbite is characterized by edema, erythema and numbness (7). These findings last for two or three weeks at which time superficial desquamation may occur. Second degree frostbite shows vesicles and blisters which involve the superficial layers of the skin. If infection does not occur the vesicles dry in from two to three weeks and leave a thin epithelial covering. Third degree frostbite involves the full thickness of the skin. A hard black scar develops which separates in about eight weeks. Fourth degree frostbite results in deep tissue necrosis and soft parts down to the bone. Amputation is necessary.

History and Physical Examination: The history reveals the exposure to cold which was associated with numbness and tingling. However numbness and tingling in itself is not necessarily indicative of tissue damage. Immediately after exposure pain is not severe; however after a few days there is burning or stinging, especially when the part is exposed to warmth; deep aching or throbbing may occur and persist for many weeks. Gangrenous areas are not painful. In the chronic stages hyperesthesia is common and increased sweating and symptoms of coldness due to sympathetic overactivity are present. Immediately after the frostbite, sweating may be absent but as improvement occurs the sweat glands show increased activity. In chronic cases the patient may complain of increased sensitivity to cold, numbness, aching pains and parasthesia even in a cool or normal environment.

Laboratory: Studies of the digital circulation in the late stages may reveal increased sympathetic vasomotor tone without evidence of organic damage as shown by normal pulsations, blood flow and skin temperatures of the digit after a posterior tibial

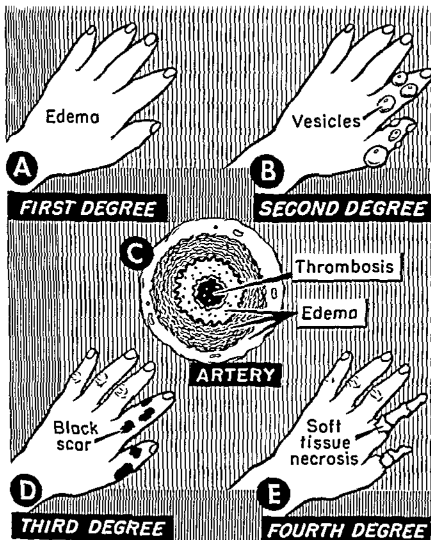


Figure 351. Clinical and pathologic findings in patients with frostbite.

nerve block. In some cases organic arterial disease can be demonstrated

Treatment: The body temperature is brought to normal as rapidly as is tolerated. Tetanus antitoxin or toxoid, gas gangrene antitoxin and penicillin may be employed. If edema is present the part may be elevated slightly. The room temperature should be kept warm and the feet kept under a cradle to avoid trauma from the blankets Third degree vesicles may be left intact until they become dry. Saline compresses may be applied to cleanse the tissues Infected areas should be kept debrided of all devitalized tissue. Penicillin is effective in most infections; however pyogenic infections generally respond to boric acid compresses Medical vasodilators may be employed. Skin grafts or amputation may be necessary. Hyperhidrosis, coldness, hyperesthesia or sensitivity to cold may require sympathectomy; however the paresthesias often are not relieved with this procedure.

Cooling of the part with ice or cold water has been advocated in the past but probably is harmful, whereas rapid warming of a frozen extremity, in animal experiments at least, is beneficial This is carried out by applying mild, moist heat to the frostbitten part while it is still frozen (8). This is continued until the part is warm Overheating may be injurious. Sympathetic block or sympathectomy is of definite value in the late stages of the disease when there is evidence of sympathetic over activity. It may be of some value when employed in the early stages of the disease as well Anticoagulant therapy has been advocated because of thrombi which have been seen in the blood stream about seventy-two hours after injury in areas which subsequently developed gangrene This has been employed clinically with variable results (9, 10).

TRENCH FOOT

This is a painful abnormality of the extremities occurring as a result of exposure of the limb to a cold, wet environment.

Age and Sex: Males and females are affected and all ages are susceptible.

Etiology: Standing with the feet in wet mud or melting snow is a common cause. The temperature is usually above freezing

and the duration of the exposure is longer than that of frostbite and varies from a few days to weeks. Reduction of blood flow through the feet may occur because of immobility of the legs or because of constricting foot gear.

Pathology: This is similar to that which occurs in frostbite (6)

History and Physical Examination: There is a history of exposure to cold water or mud with the symptoms of swelling of the feet which occur during exposure. The feet feel cold, numb and painful. "Pins and needles" are common on the plantar surfaces. If the foot is examined early it is cold, pale, cyanotic and edematous. When the part is warmed it becomes intensely red Vesicles on the dorsum of the foot filled with hemorrhagic or clear fluid may be present. Secondary infection is common and desquamation may be present or may occur subsequently (11). Gangrene is not common Weakness of toes may occur or atrophy, fibrosis and contractures may develop in severe cases The primary finding in chronic cases may be evidence of nerve damage, for example, hyperesthesia, hypesthesia or sympathetic overactivity, for example hyperhidrosis and coldness (figure 352)

Laboratory Work: In mild cases the blood flow is not interferred with but in advanced cases the flow is diminished.

Treatment: (See frostbite).

IMMERSION FOOT

This is an abnormality which results from soaking the feet for long periods in cool water.

Age and Sex: All ages and both sexes are susceptible

Etiology: Soaking of the feet in cool water produces the syndrome which occurs in patients taken from life rafts after ship wrecks or plane crashes.

Pathology: This is similar to that of frostbite

History and Physical Examination: There is hypesthesia, numbness, coldness and pain (12) A constricted and hyperemic stage is recognized (figure 353). During the constricted stage the limb is cold and pale. In the hyperemic phase erythema, edema, vesiculation and in some cases gangrene may occur. Sensory loss is common because of nerve involvement (13). In chronic cases there is burning or aching pain in the feet. Motor

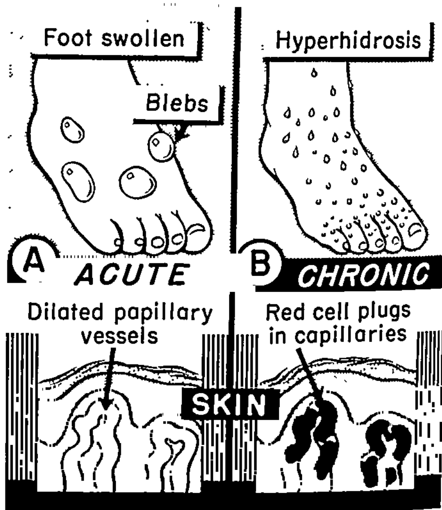


Figure 352. Acute and chronic stages of trench foot.

paralysis may result in a slapping gait. Initially there is anhidrosis and this is later replaced by hyperhidrosis.

Laboratory: In some chronic cases diminished circulation in the toes can be demonstrated plethysmographically.

Treatment: The treatment is not significantly different from that of frostbite.

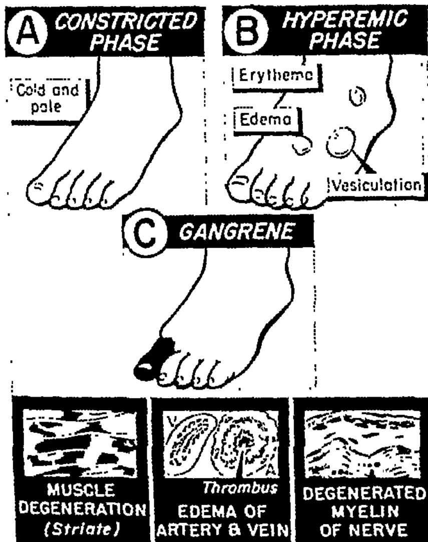


Figure 353. Constricted (A), and hyperemic (B), phases which occur in patients with immersion foot

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CHAPTER 36

Ainhum

DACTYLOLYSIS SPONTANEA

THIS IS A DISEASE characterized by the formation of a fibrous band of tissue around the toe with ischemic changes distal to the band (1, 2). The term, which is derived from an African word, means "to saw" (3).

History: Clark in 1860 first described the disease in the Western Hemisphere. By 1944 two hundred cases had been reported (4, 5).

Sex and Race: The disease occurs primarily in dark skinned males especially in Negroes (3).

Etiology: This has not been established with certainty. In certain cases the following etiologies have been suggested: infections, e.g., syphilis; localized sclerosis; constricting scars and injury by Chigoes (Tunga penetrans) (3, 4, 5, 6).

History and Physical Examination: The patient complains of pain in the toe. Often the disease is bilateral. A constricting band usually involves the fifth toe and results in swelling, pain and congestion (figure 354). Gangrene and auto-amputation may be present and secondary infection is common.

Laboratory: Plethysmographic studies show a good blood flow (4).

Treatment: Symptomatic treatment may be employed allowing auto-amputation to occur. The fibrous ring may be divided down to the periosteum which may relieve congestion. A metatarsal phalangeal disarticulation with removal of the metatarsal bone may be necessary. Medical vasodilators and sympathectomy are not effective.

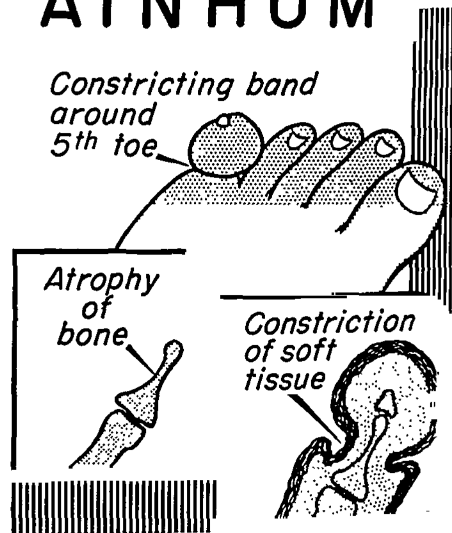


Figure 354. Typical constricting band around fifth toe with bone atrophy in a patient with ainhum.

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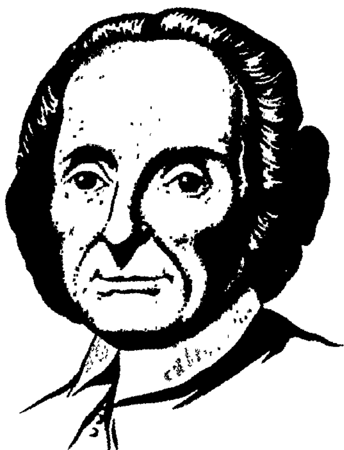


Figure 355 Giovanni Maria Lancisi, 1654 to 1720 He was the first to describe luetic aneurysms of the aorta He made studies of aneurysms of various vessels through clinical and gross pathologic observation which extended over a period of years and which were described in his book, De Aneurysmatibus published posthumously in 1745.

CHAPTER 37

Arterial Aneurysms

AN ANEURYSM is an abnormal, usually permanent, dilatation of a blood vessel resulting often from localized weakness of the wall of the artery.

History: Aneurysms were described by Galen as early as the second century A.D. Galen of Pergamon, born in 130 A.D., was physician for the gladiators. These men suffered severe wounds which gave Galen the opportunity of observing human anatomy and physiology. Lancisi (figure 355) born in 1654 made numerous studies on aneurysms and wrote extensively on the subject (1).

Mechanisms Producing Aneurysms: An aneurysm results usually from the following: 1) a localized weakness of the vessel wall; 2) an increased pressure in the lumen of the vessel, 3) increased blood volume as in hypertension with congestive failure, 4) increased cardiac output as occurs from high output cardiac failure, and 5) a decrease in the amount of support to the vessel by other structures. Once an aneurysm begins to form it often progresses rapidly, following Laplace's law which states that the tension on the vessel wall increases rapidly as the diameter of the vessel increases (figure 74). Thus one would expect large vessels to become aneurysmal more frequently than small ones because of their increased diameter which is consistent with the high incidence of aneurysms of the aorta as compared with those of the arteries of the limbs (2)

Etiology: Aneurysms are 1) true, 2) false, 3) acquired or 4) congenital.

True Aneurysms (figure 356): These are dilatations of the arterial wall and the wall of the artery is intact.

False Aneurysms (figure 356): Here the arterial wall is interrupted and the aneurysmal sac consists of the surrounding tissues such as muscle or subcutaneous tissue.

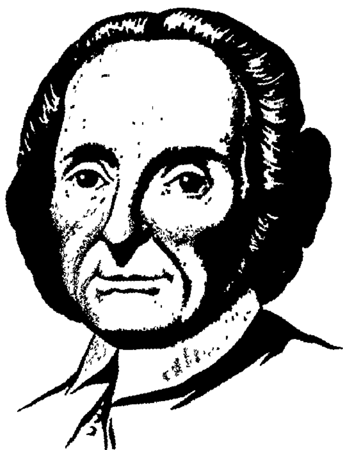


Figure 355 Giovanni Maria Lancisi, 1654 to 1720. He was the first to describe luetic aneurysms of the aorta. He made studies of aneurysms of various vessels through clinical and gross pathologic observation which extended over a period of years and which were described in his book, *De Aneurysmatibus* published posthumously in 1745.

Congenital Aneurysms (figure 356): These usually involve the internal carotid artery or the circle of Willis and are seen often with other vascular anomalies (3). The medial coat of the vessel often is thin and underdeveloped or even absent. Rupture and hemorrhage may occur.

Acquired Aneurysms (figure 356): These may be secondary to: 1) arteriosclerosis; 2) trauma; 3) syphilis; 4) tuberculosis, 5) typhoid; 6) periarteritis nodosa; 7) cystic or medial necrosis; 8) dissection of the aorta; 9) diabetes mellitus, 10) lead poisoning; 11) gout; 12) malignant invasion of an artery; 13) fungus infections; 14) burns, 15) x-ray irradiation; 16) radium; 17) arteritis of any cause, and 18) embolism. Acquired aneurysms are common in the aorta, subclavian, iliac, femoral and popliteal arteries

Arteriosclerotic, dissecting, syphilitic, mycotic, necrotizing arteriolytic and embolic aneurysms will be discussed here

ARTERIOSCLEROTIC ANEURYSMS: These are a common complication of generalized arteriosclerosis.

Sex and Age: They are more frequent in men than in women and occur usually after the age of forty-five.

Etiology: Arteriosclerotic aneurysms occur from the causes already mentioned. They occur commonly in the abdominal aorta below the renal arteries; common or external iliac; femoral or popliteal arteries. In the thoracic aorta arteriosclerotic aneurysms are often fusiform. In the abdominal aorta or popliteal artery they may be fusiform or saccular. Most aneurysms due to arteriosclerosis develop slowly because of the gradual weakening of the vessel wall which occurs as the media becomes thin (4); however some aneurysms appear acutely with strain. The latter is not uncommon in the popliteal artery which becomes aneurysmal suddenly with bending of the leg or during strain such as the pushing of heavy objects.

Pathology: Often examination of the aneurysm reveals atherosclerosis with hemorrhage into plaques with fibrosis, calcification, ulceration of the intimal surface and clot formation.

History and Physical Examination: Symptoms may be entirely absent; however the patient may complain of pain if the aneurysm is leaking or expanding rapidly. Often the first complaint is a pulsating mass which may be prominent in the abdominal region.

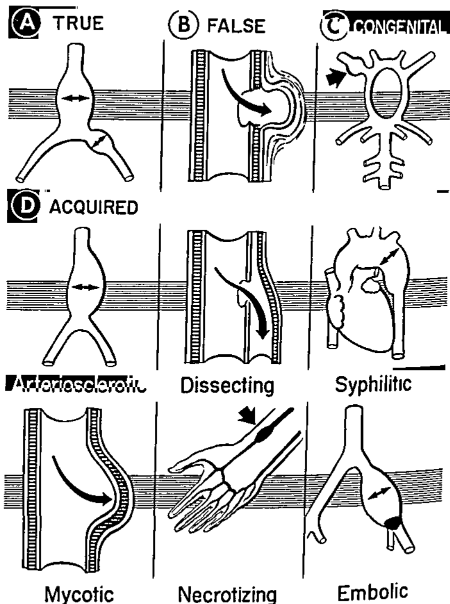


Figure 356 Aneurysms may be classified as true (A) or false (B), or as congenital (C) or acquired (D).

the observation that if an aneurysm can be made to occlude slowly, collateral circulation will take over to nourish the parts distally. A polythene covering is applied around the aorta with or without chemical irritation and as a result a fibroblastic proliferation develops. This technique is not uniformly successful.

Intravascular Wiring. This has been largely replaced by arterial homografts. The wire itself may retard blood flow, enter the heart or favor the deposition of platelets which results in purpura

Wrapping With Wire: This is not generally successful because of necrosis of tissue by the wire.

Babcock's Operation: This is based on the principle that decreasing the resistance peripheral to an aneurysm allows a rapid flow through it which decreases the lateral pressure on the aneurysmal wall For aneurysms of the ascending aorta an anastomosis of the proximal end of the carotid artery to the cardiac end of the jugular vein is made The peripheral resistance and intra-aneurysmal pressure are thereby reduced. This operation is seldom performed (11).

DISSECTING ANEURYSM: This is an abnormality of an artery in which a break in the intima occurs with splitting of the wall.

Etiology: Arteriosclerosis or cystic medial necrosis are common causes. Hypertension may be a precipitating factor.

Pathology: The dissection usually begins with a tear in the ascending aorta but may extend partly to completely around the circumference of the artery. The dissection may extend proximally to the orifices of the coronary arteries or to the femoral arteries.

History and Physical Examination: There is often severe pain in the back which migrates from the thoracic to the lumbar region as the dissection takes place distally. This is associated with weakness, coma or hemiplegia. Pulsations of the innominate, carotid, subclavian or femoral arteries may be absent depending upon the exact location of the dissection. The blood pressure often is maintained which is in contrast to that which occurs with myocardial infarction. Pulsations of the sternoclavicular joint, an aortic diastolic murmur or ecchymosis of the abdominal wall may occur.

The physical signs are usually an expansile pulsation felt by placing one hand on each side of the aneurysm (figure 311). A bruit over the aneurysm is common. The peripheral pulses may be normal, increased or decreased.

Laboratory Findings: Fluorscopic examination of the chest may reveal an enlarged thoracic aorta which may or may not pulsate. X-ray of the abdominal aorta may show aortic enlargement with calcification of the wall of the aneurysm. The vascular studies often show large pulse waves in the legs and toes below an abdominal aneurysm; however the pulsations are reduced when arterial obstructions are present. Aneurysms may show clearly by aortographic or arteriographic techniques.

Treatment: The various treatments include: 1) resection and end to end anastomosis; 2) removal of the aneurysmal sac; 3) arterial homografts; 4) vein grafts; 5) obliteration of the aneurysm; 6) perianeurysmal irritation; 7) intravascular wiring, 8) wrapping with wire; 9) lowering of resistance peripheral to the aneurysm.

Resection and End to End Anastomosis: This is the ideal form of treatment and can be carried out in many cases of coarctation of the aorta and after some traumatic lesions to arteries (5).

Removal of the Aneurysmal Sac. Often the orifice of the aneurysm is small which allows the entire aneurysmal sac to be *removed and the artery to be repaired (6).*

Arterial Homografts: These are especially suited for repairing aneurysms of the abdominal aorta (7). Prosthetic plastic tubes (*Dacron*, etc.) have been employed with some success.

Vein Graft· This may be used for small arteries but *should not* be used for large arteries because dilatation occurs easily when the diameter of the vessel is large. Dilatation may be prevented by supporting the vein by surrounding tissue.

Obliteration of the Aneurysm: Obliteration of the aneurysm can be accomplished with a muscle implant (8, 9). The aneurysmal sac is opened and all clots and debris are removed. The main artery entering and leaving the sac is ligated. The sac is left in place and a muscle flap is sewn over the aneurysm to obliterate it. The collateral circulation is left intact.

Perianeurysmal Irritation: This has been used at times for the treatment of thoracic aneurysms (10). The technique is based on

aneurysm from a tumor. Serologic reactions for syphilis usually are positive.

Treatment: Adequate antisyphilitic therapy should be provided (10). DeBakey has suggested resection and repair of certain saccular thoracic syphilitic aneurysms if the sac involves one side of the artery only (13).

Prognosis: This is poor. Death occurs from rupture of the aneurysm into the trachea, bronchus, pleural or pericardial cavity, esophagus, vena cava or elsewhere.

MYCOTIC ANEURYSMS These are aneurysms due to various infectious diseases other than syphilis Tuberculosis, bacterial endocarditis, pneumococcus pneumonia, typhoid fever and septicemia are causes (15, 16, 17, 18) These diseases weaken the arteries and aneurysms form especially where bending is frequent. The popliteal artery is commonly involved In certain cases bacteria may reach the artery wall by way of the vasa vasorum and an arterial abscess forms. The wall weakens and aneurysms form.

NECROTIZING ANEURYSMS OF ARTERIES Necrosis of arteries from any cause causes aneurysms (19). The diseases characterized by necrotizing arteritis are: 1) periarteritis nodosa; 2) hypersensitivity angiitis; 3) rheumatic arteritis, 4) allergic granulomatous arteritis, and 5) temporal arteritis. The term necrotizing angiitis includes all diseases characterized in their fully developed stage by inflammatory reaction and fibrinoid necrosis. The term does not designate etiology and includes arteries or veins of any size. The pathologic picture includes fibrinoid necrosis, fibroblastic proliferation, capillary budding and collagen scars. Periarteritis nodosa is prone to form aneurysms

EMBOLIC ANEURYSMS: An embolism is associated with increased strain on the arterial wall proximal to the site of obstruction. When the artery was patent prior to the embolus the blood pressure was exerted in forward and lateral directions. After embolization the entire force of the cardiac contraction is exerted in a lateral direction which increases the tension on the artery wall.

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Laboratory Work: Serial x-rays of the chest show progressive dilatation of the aorta. Leukocytosis is common and progressive anemia occurs if internal hemorrhage takes place from rupture through the aortic wall into the surrounding tissues

Treatment: Relief of pain should be provided which may improve arterial spasm. The patient should be kept at rest and his pressure kept low with reserpine or other antihypertensive drugs. DeBakey (12, 13) suggests dividing the aorta and resuturing the outer portion thus producing an intraluminal outlet for the blood.

Prognosis: This is grave. Over half of the patients die in the first few hours or days; however healing may occur in a small percentage of patients but recurrences are common.

SYPHILITIC ANEURYSMS: These occur in the thoracic aorta in the arch, ascending or descending limb. Aortic insufficiency or stenosis of the orifices of the coronary arteries by syphilitic plaques may be present also (14). The aneurysms often are saccular but may be fusiform.

Etiology: Treponema pallidum is the cause of the weakening of the aortic wall. The spirochetes can be demonstrated in the aortic wall in some cases.

Sex, Age and Race: The disease is more common in men than in women and occurs usually after the age of twenty-five years. The disease is common in Negroes but affects white and other races.

History and Physical Examination: Pain may be present in the left scapula or substernally and is due to pressure of the aneurysm on bone and on surrounding structures which produces hoarseness, cough and dysphagia A heaving chest wall may be present. If the coronary orifices are involved anginal pain of effort is present. A systolic murmur is common over the aneurysm. There is retrosternal dullness to percussion. A tympanitic aortic second sound may be present

Laboratory Work: X-ray and fluoroscopic examinations reveal a pulsating mass connected with the aorta; however pulsations may not be present when a large blood clot is present in the aneurysm. An angiogram may be necessary to differentiate an

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CHAPTER 38

Arteriovenous Fistulas

THESE ARE DIRECT communications between an artery and a vein which allow blood to pass to the venous circulation without passing through the capillary bed.

History: William Hunter in 1757 was one of the early men to describe these anastomoses and was the first to appreciate the true nature of the communication (1). Sir Thomas Lewis made studies of arteriovenous fistulas also (figure 357).

Classification: Arteriovenous fistula may be congenital or acquired.

CONGENITAL FISTULAS

These are present especially on the acral portions of the limbs.

Etiology: Embryologically the arteries and veins arise through differentiation from a common vascular plexus. Some of these vessels become arteries while others become veins and at certain stages of development numerous communications are present. The persistence of these communications results in multiple arteriovenous fistulas (2, 3).

Sex and Age: They occur in men and women of all ages.

Types: A wide variety of anatomic types are seen and are as follows:

A: The most common type consists of multiple arteriovenous communications which involve only the superficial small vessels and is similar to the capillary hemangioma (figure 396). B: In addition to the above a single larger arteriovenous communication may be present. C: An artery may give rise to numerous small branches and empty into a venous hemangioma. This may be termed a cirsoid aneurysm. D: A vascular tumor type is characterized by an artery which gives rise to numerous tufts of small



Figure 357. Sir Thomas Lewis, 1881 to 1945. He was a student of Sir James Mackenzie He made notable contributions to knowledge concerning the peripheral circulation. He studied vascular reactions to injury and made studies on erythermalgia, Raynaud's disease, ergot poisoning, causalgia, arterial embolism, arteriovenous fistulas and on the effects of environmental temperature on blood vessels of the skin and other tissues.

thrill may be present. The thrill and murmur may be eliminated by pressure over the vein proximal to the fistula. Branham's sign is characteristically present, that is temporary closure of the fistula (by manual compression) produces slowing of the heart rate with an increase in diastolic pressure (7) The drop in heart rate is associated with the rise in arterial pressure and the fall in venous pressure. *This reflex can usually be abolished by atropine.* If the fistula is as large or larger than the artery from which it arises *these signs are prominent* (8) *Usually congenital aneurysms are* small and these signs are not present

Laboratory: X-rays of the heart show cardiac enlargement to the right and to the left. Congestion of the lung fields may be present if left heart failure is present Plethysmographic records usually show increased pulsations and blood flow distal to the fistula (figure 358) although occasionally a decrease may be present. Segmental plethysmograms likewise show increased pulsations as a rule over the fistula The blood volume and cardiac output usually are increased Venous pulsations are large and venous blood temperature and oxygen saturation are increased over normal. Cardioangiography is of value if the anastomoses are in the chest Aortography is employed when the fistula is in the abdomen or pelvis. Angiography is of value if the fistula is in an extremity (figure 200). A rich collateral circulation is observed around long standing arteriovenous fistulas (9) A venogram may show the fistula clearly (figure 213) A blood pressure cuff may be inflated to above systolic pressure on various segments of the limb and samples of blood taken from the vein and compared for oxygen content. In this way the fistula may be located (10, 11).

ACQUIRED FISTULAS

The findings are essentially the same as those of the congenital fistulas; however increased blood volume, cardiac enlargement, cardiac failure and thrills are more common with acquired fistulas whereas hemihypertrophy is more common with congenital fistulas.

Sex and Age: Both sexes and all ages are affected

Etiology: Trauma is the usual cause although neoplasms or infections may cause fistulas (7, 12, 13)

arterioles and E: A rare type occurs in which there is a single direct communication between a large artery and vein associated with *dilated varicosities (4). The fistulas may be located in the* head, in the bones of the extremities or in the lungs. The vessels of the trunk and viscera are only rarely involved.

History and Physical Examination: Symptoms usually begin in childhood or in infancy. The complaint may be that of increased growth of a leg or attention may be paid to the normal leg and the complaint is that of decreased growth of a limb. Abnormal pulsations of veins, prominence of superficial veins or temperature differences between limbs may be the complaint. If the fistulas are in the head the complaint may be that of vertigo or headache. A systolic or continuous murmur over the fistula may be encountered. The blood pressure may be abnormal if the fistula is large. There is a large decrease in diastolic pressure, a small decrease in systolic pressure and an increase in pulse pressure because the fistula serves as a leak between artery and vein (5,6). Systole is of short and diastole of long duration. Systolic blood pressure results from the force of the cardiac output acting against *peripheral resistance. Diastolic pressure results from the elastic* recoil of the artery forcing blood against peripheral resistance. The effect of the fistula is greater on the diastolic pressure than on the systolic pressure because the duration of diastole is longer than that of systole. An increase in local venous pressure may be detected by palpation or by measurement (figure 224). Arterial pulsations may be felt or recorded from the veins. Arterialization of the venous blood is suggested by a warm vein as compared with a cooler companion vein. The Bainbridge reflex may be positive (that is an increase in heart rate results from the low blood pres*sure in the carotid sinus and aorta).* Right heart failure may be present with edema of the extremitis, elevated venous pressure, distended neck veins and enlargement of the liver. This is due to the increased blood volume with increased return of blood to the right heart. Left heart failure develops later as a result of pumping an increased volume of blood and attempting to maintain the systemic pressure even in the presence of the "leak." Rales in the chest will then be present. A machinery murmur accentuated during systole may be heard over the fistula and a systolic

thrill may be present. The thrill and murmur may be eliminated by pressure over the vein proximal to the fistula. Branham's sign is characteristically present, that is temporary closure of the fistula (by manual compression) produces slowing of the heart rate with an increase in diastolic pressure (7) The drop in heart rate is associated with the rise in arterial pressure and the fall in venous pressure. This reflex can usually be abolished by atropine. If the fistula is as large or larger than the artery from which it arises these signs are prominent (8). Usually congenital aneurysms are small and these signs are not present

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History and Physical Examination: Often there is a history of trauma which may be slight or severe. Enlargement of the limb is not great. A murmur and thrill may be present over the fistula. The veins may be distended and may be pulsating and Branham's sign is positive.

Laboratory Work: The vascular studies show increased pulsations over the fistula. Arteriograms or venograms may show the site of the fistula (figure 200). High pulsations, a high oxygen content, and an increased pressure and temperature may be recorded from the involved vein.

Treatment: If the fistula is traumatic, time should be allowed for collateral circulation to develop, after which the fistula should be excised and the circulation reestablished if possible (14, 15, 16, 17, 18). Three methods of treatment are as follows:

1) *Removal of the Fistula with Repair of the Artery and Vein.* The artery and vein are dissected free. The fistula is removed and the continuity of the artery and vein reestablished. Muscle is placed between these vessels to prevent recurrence of the fistula.

2) *Arterial Repair and Division and Suture of Vein:* When necessary arterial homograft or autogenous vein graft may be employed

3) *Ligation of Arteries and Veins* The fistula and a segment of the artery and vein are removed The ends of the arteries and veins are tied This procedure is carried out if the above procedures cannot be performed. Usually tests to demonstrate the presence of collateral circulation should be carried out first to be sure that the collateral vessels can maintain the circulation to the limb.

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ARTERIOVENOUS FISTULA

Congested lung field

Large heart

Pulse high

Pulse normal height

FISTULA

Figure 358. A large heart, congested lung fields and high pulsations over an AV fistula occur if the fistula is large.

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Figure 359. Maurice Raynaud, 1834 to 1881. He was the son of a university professor and he received his M D. degree in 1862. He was elected to the Academy of Medicine and presented his description of "Local Asphyxia and Symmetrical Gangrene of the Extremities" as his inaugural thesis.

CHAPTER 39

Raynaud's Disease

THIS IS A FUNCTIONAL disease of the arteries and arterioles of the acral portions of the limbs characterized by attacks of color changes and discomfort which occur as a result of a cold environment or nervousness. Raynaud's disease may be primary or secondary.

PRIMARY RAYNAUD'S DISEASE

This disease involves the digital arteries and arterioles and is characterized by the Raynaud's phenomenon (attacks of typical color changes) and occurs commonly in nervous young women (1).

Sex and Age: The disease is more common in females than in males (5 to 1) and it usually begins before the age of forty. In certain patients a family history of Raynaud's phenomenon may be obtained.

Etiology: The disease may represent a disturbance in the conditioning mechanism of the body wherein conditioning occurs too easily or persists too long a period of time. A state of hyperreactivity of the blood vessels to cold, nervousness and other stimuli is common. Emotional instability is the rule and exacerbations of the disease occur during emotional stress and at the time of the menses.

Pathology (figure 360): In the early stages there is no evidence of organic disease; however in the late stages endarteritis obliterans is present. Microscopic sections of tissue from the digits show thickened intimas, split internal elastic membranes and thrombi in various stages of recanalization (2).

Pathologic Physiology: The color changes which take place in the digits are related to the presence of vasoconstriction and

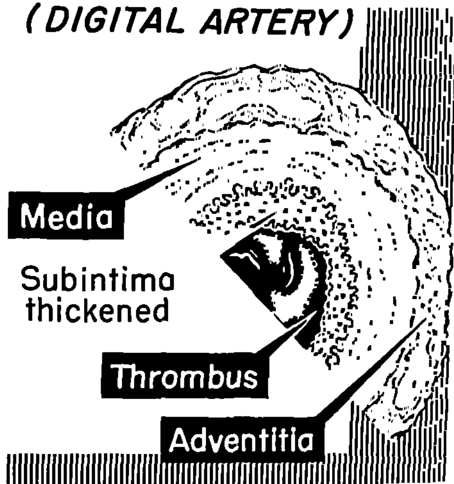


Figure 360. Typical pathologic findings of a digital artery of a patient with primary Raynaud's disease.

vasodilatation of the arterioles in the skin and to the velocity of blood flow through the vessels. Studies with the capillary microscope show that when the fingers are pale the capillaries are without red cells due to constriction (figure 275A). When blue the capillaries are full of reduced blood due to stasis (figure 275B) and when red fast moving oxygenated blood is present (figure 275C) (3, 4).

History and Physical Examination: The patient complains of attacks of color changes in the fingers which are associated with paresthesia or pain. Numbness, tingling, burning and a feeling of tightness or pins and needles occur during attacks of vasoconstriction when the digits are white or blue Subjectively the hands feel flushed and warm when they are red. During ischemic periods sensory acuity is diminished and swelling of the fingers occurs. Objectively the fingers are cold when they are white or blue and are either warm or cool when they are red Attacks are more frequent and severe during a cold winter than during a warm summer. With repeated attacks thickening of the skin occurs and ulcers appear at the tip of the fingers. The ulcers extend often under the nail causing the nail to pull away from the nail bed. The nail is curved in its longitudinal direction and small infarcts may be seen in the nail bed and in the skin (figure 361).

Diagnosis: A history of color changes of the digits, which may be u[illegible] in th[illegible] disease should be ruled out. All of the large arteries should pulsate normally. Tests for the patency of individual vessels such as the radial and ulnar arteries should be made (figures 181, 182). There should be no elevational pallor or dependent rubor in the early or vasospastic stage; however these findings are present during the late stage of the disease when organic involvement of the digital arteries has occurred (5). The following criteria make the diagnosis most secure: 1) color changes of the digits excited by cold or emotion; 2) involvement of both upper extremities, however the disease may be unilateral, 3) gangrene of small cutaneous areas, and 4) absence of primary organic disease such as thromboangiitis obliterans.

Laboratory Studies: The skin temperature test for cold sensitivity is positive (figure 362), and skin temperatures recorded with the patient at rest often show abnormally large and rapid temperature fluctations. The vascular studies show normal arterial pulsations at ankles and wrists In advanced cases the pulsations at the fingers are abnormal due to organic arterial involvement of the digital arteries (figure 363). Often the exact location of an obstruction in a digital artery may be detected by making appro-

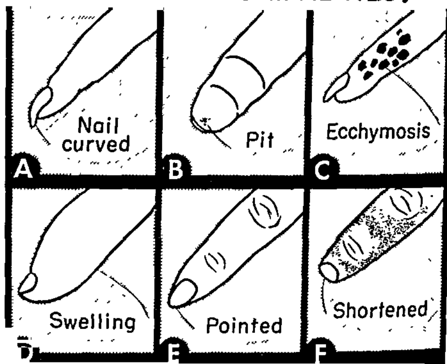


Figure 361. Typical appearance of fingertips of patients with primary Raynaud's disease Beaking of the fingernail (A), pitting of the fingertip representing infarcts (B), echymotic areas representing localized areas of capillary damage (C), swelling which occurs often during or after attacks which represent increased capillary permeability (D), atrophy of the fingertip with pointing of the digit (E), absorption of bone of the distal portion of the terminal phalanx (F).

priate measurements at various sites on the digit (figure 132). Decalcification of bone (figures 208, 209) may be seen on x-ray.

Differential Diagnosis: The disease must be differentiated from secondary Raynaud's disease caused by thromboangiitis obliterans, arteriosclerosis obliterans and scleroderma, etc (6, 7).

Thromboangiitis Obliterans: This is more common in men than in women. It usually involves the lower extremities first and the

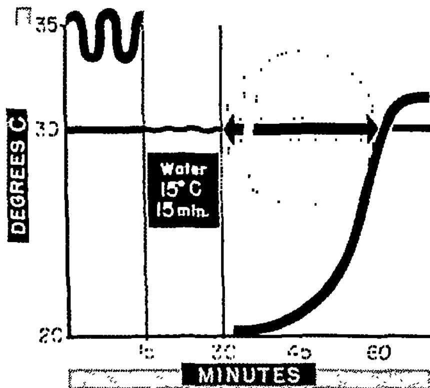


Figure 362 Cold sensitivity test. With Raynaud's disease, after cooling the hand in water 15 degrees C for fifteen minutes, the hand warms up *more slowly than normally*

upper extremities later. The disease usually involves one or two digits and is not necessarily bilateral. It is frequently associated with thrombophlebitis and neuritis. Occlusion of the ulnar artery is common.

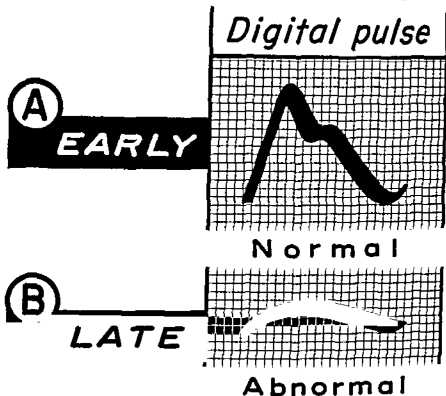


Figure 363. With primary Raynaud's disease the pulsations of the digits may be normal early but late in the disease they are abnormal and indicate the presence of organic involvement of the arteries. Usually the pulsations from the arteries of the arms and legs are normal

Arteriosclerosis Obliterans: In this disease the color changes occur in only one or two digits Usually pallor is more outstanding than cyanosis. Usually males over the age of fifty years are involved. Evidence of arteriosclerosis is present elsewhere; for example obstructions may be present in the aorta, iliac, femoral or popliteal arteries. The lower extremities usually are involved before the upper extremities

Scleroderma: The skin of the face, neck, hands and legs is usually involved. Thickening of the skin may precede the color

changes in the digits. The esophagus, heart, lungs and other organs may be involved.

Treatment: This is medical and surgical.

Medical Treatment: The patient should avoid cooling of the hands or of the body and should wear mittens and warm stockings. The room temperature should be warm.

Tolazoline hydrochloride (Priscoline®) 25 mg three times a day after meals is helpful during the cold weather or when ulcers are present.

The DH ergot alkaloids (Hydergine®) 5 mg sublingually four times daily, are of value when the upper extremities are involved and are of less value for the lower extremities The agents have a central sedative effect which allay nervousness and have an adrenolytic effect which results in slight warming of the hands.

Glycerol trinitrate (2 per cent nitroglycerin ointment, Nitroglan®) rubbed into the skin of the involved fingers in the nonulcerated areas two to three times daily produces slight warming of the skin and should be employed If the dose is too large headaches may occur (8)

Beta pyridyl carbinol tartrate (Roniacol®) in large doses (150 mg of the long acting tablet three times a day after meals) is helpful for the upper extremities.

Phenoxybenzamine (Dibenzyline®) 10 mg three times a day is of value as a strong adrenolytic agent.

Surgical Treatment. Sympathectomy in which the second cervical ganglion is removed is of definite value if it is carried out in patients with functional vasoconstriction of neurogenic origin when organic arterial disease is minimal Partial return of sympathetic function is anticipated within one to two years after sympathectomy, however the clinical results are fair from five to ten years after surgery in a significant percentage of patients (9, 10, 11).

SECONDARY RAYNAUD'S DISEASE

This is a vascular disorder characterized by attacks of color changes in the skin which are secondary to known disease states or are secondary to known causes.

Etilogy: The etiology may be: 1) trauma, for example pneumatic hammer disease (12, 13); 2) intoxications, due to ergot, lead or arsenic (14, 15); 3) exposure to cold, for example, frostbite, immersion foot, cold agglutination of erythrocytes or cryoglobulinemia (16, 17, 18); 4) neurovascular syndromes of the shoulder girdle (19), such as anterior scalenus, hyperabduction, costoclavicular, malposition, cervical rib or band or thoracic outlet *syndromes; 5) diseases such as thromboangiitis obliterans,* arteriosclerosis obliterans, livedo reticularis, arteritis, collagen diseases or paroxysmal hemoglobinuria.

Sex and Age: The sex and age distribution depends upon the underlying disease. If thromboangiitis is the cause young males predominate. If arteriosclerosis is the cause, elderly males predominate, and if disseminated lupus erythematosus is the cause, young females predominate.

History and Physical Examination: The symptoms and signs are usually those of the basic disease which is associated with the occurrence of attacks of color changes of the digits.

Diagnosis: The diagnosis is made from the presence of the Raynaud's phenomenon, but in addition the findings of the basic disease are present. For example, if the Raynaud's phenomenon occurs in a patient with arteriosclerosis often occlusion of the abdominal aorta or other major vessels is present. If the phenomenon occurs in a patient with thromboangiitis obliterans the ulnar artery may be occluded with involvement of veins and nerves.

Differential Diagnosis: Secondary Raynaud's disease should be differentiated from primary Raynaud's disease. The latter occurs in nervous young women who do not have involvement of large arteries and who do not show evidence of disease capable of producing the Raynaud's phenomenon.

Treatment: This is similar to the treatment of primary Raynaud's disease; however the basic disease is treated also (vide supra).

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CHAPTER 40

Acrocyanosis

ACROCYANOSIS is a benign, functional, vasospastic state characterized by a persistent uniform cyanotic discoloration of the skin of the hands and feet

History: The term "acrocyanosis" was first applied by Crocq (1) and an adequate description of the disease was given by Cassirer in 1912 (2). Since, the disease has been studied by Lewis and Landis and others (3, 4, 5).

Etiology: This may be an increased activity of the sympathetic nervous system; however vasoconstriction due to circulating humoral agents or a high intrinsic tone of the muscular media of vessels may be the cause. Aggravating factors are a cold environment and nervousness.

Age and Sex: The disease is common in young and middle aged individuals and is four times as common in women as in men.

Pathologic Physiology: The essential abnormality in some cases is excessive arteriolar constriction, which occurs at ordinary environmental temperatures. The cyanosis is abolished by elevation of the part and by sleep The latter suggests that nervous or endocrine factors which are present during the day are responsible. The constriction is associated with capillary and venous dilatation, stasis of blood and overreduction of the hemoglobin in the subcapillary venous plexus, which imparts a cyanotic color to the skin (6). The cyanosis is not uniform but is present in scattered areas. Large capillary loops occurring in increased numbers have been described in the nail bed (7, 8). Although it is possible that constriction of veins could produce the discoloration, this is unlikely in view of the observation that elevating the cyanotic extremity abolishes the cyanosis (3) After pressure on a cyanosed area the color returns from the periphery of the point of pressure rather than from below, as occurs frequently in normal skin.

History and Physical Examination: The only symptoms usually are persistently discolored cold, often wet hands at a comfortable room temperature (figure 364). The patient frequently consults the doctor for cosmetic reasons. The hands are involved in the abnormal process to a greater extent than the feet. Swelling and

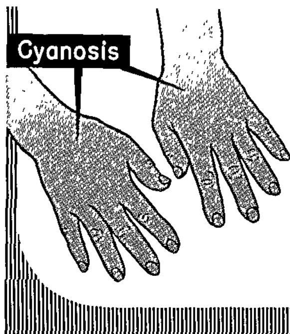


Figure 364 Typical areas of vasomotor change in patients with acrocyanosis

thickness of the fingers occur rarely. When the hands are exposed to a cold environment the cyanosis increases, provided the temperature is not below 10° C which produce redness owing to arteriolar injury and dilatation and retarded deoxygenation of the blood. The dorsal surfaces of the hands and feet often are dry when the volar surfaces are sweating freely.

Differential Diagnosis: The disease should be differentiated from Raynaud's disease, scleroderma, arteriosclerosis obliterans, pernio and livido reticularis.

Raynaud's Disease: This produces attacks of color changes which last 15 to 60 minutes, gangrene, nail changes and pitting infarcts of the fingers. These findings are not present in acrocyanosis.

Scleroderma: The thickening of the skin, calcification of skin and visceral involvement, stiffening of joints, pigmentation and depigmentation which are characteristic of scleroderma do not occur with acrocyanosis, however in rare instances edema of the fingers is encountered.

Arteriosclerosis Obliterans: Here there is evidence of involvement of large arteries, such as the aorta, iliac, femoral or popliteal, which does not occur with acrocyanosis

Pernio: This disease involves primarily the legs and not the acral portions of the limbs. Pernio is worse in the winter than in the summer and is associated with itching and burning with redness of the tissues.

Livedo Reticularis: Usually the legs are involved as well as the acral regions of the limbs The skin is mottled and ulcers may be present. Livido reticularis may occur in patients with acrocyanosis.

Treatment: The body should be kept warm by wearing mittens, wool lined shoes or slippers, wool stockings, slacks, coats, etc. Mental relaxation and freedom from worry are important. Tranquilizing drugs such as meprobamate are important. Dibenzylene® helps dry the hands and increases skin temperature. Roniacol®, Priscoline® and Hydergine® are of slight benefit The disease usually is not severe enough to warrant sympathectomy, however this has been successful in a few cases

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CHAPTER 41

Livedo Reticularis

THIS IS A FUNCTIONAL vasospastic disorder in which cyanosis takes the form of a mottled, blotchy pattern of the skin.

History: The term livedo reticularis apparently was first used by Kaposi. A good clinical description of the disease was presented by Williams and Goodman in 1925 (1).

Age, Sex and Race: The disease affects primarily young women under the age of 40. There is no racial predilection.

Etiology: This is unknown; however the disease is common in patients with nervous instability.

Clinical Types (figure 365): *Type I,* called cutis marmorata which is a mottling of the skin, occurs on exposure to cold and disappears in a warm environment. *Type II* is livedo reticularis idiopathica in which the discoloration persists in a warm environment as well as in a cool one and the abnormality is not secondary to other diseases. *Type III* is livedo reticularis symptomatica in which the discoloration persists in a warm environment and the process is associated with other diseases, for example periarteritis nodosa (1).

Pathology (figure 365): The characteristic abnormality is a constriction either organic or functional of the arterioles of the skin with dilatation of the capillaries and venules (2). Sections of the skin reveal the presence of organic arteriolar disease with intimal proliferation and perivascular infiltration (3).

History and Physical Examination: Patients with type I disease usually have no symptoms while patients with type II and type III disease complain of coldness, itching, discoloration, aching, paresthesias or ulcerations of the skin. Ulceration may involve the skin of the extremities or acral portions of the extremities Discoloration is present, usually on the legs and feet but may in-

LIVEDO RETICULARIS

TYPES

I ··· Color disappears on warming.

II - III · Color does not disappear on warming.

MOTTLING
DISCOLORATION OF ARMS AND LEGS

SKIN SECTION

lymphocytes

Intimal proliferation

Figure 365. Clinical and pathologic findings in patients with livedo reticularis

volve the arms and hands and forms a reticulum due to the capillary dilatation which may be observed with a hand lens (4). When ulcers appear they occur in the cyanotic areas first. Often the circulation in the center of the dilated capillary rings appears relatively normal.

Laboratory Tests: The vascular tests for the patency of large arteries are normal. The circulation to the toes may be abnormal after a posterior tibial nerve block with types II and III disease but is normal with type I disease.

Treatment: Type I livedo reticularis requires no special treatment. Type II disease should be treated, especially if ulcer formation is imminent or present. Lumbar sympathetic blocks could be carried out to determine the amount of vasodilatation which can be produced with this technique. If there is a satisfactory increase in circulation after a posterior tibial nerve block and the cyanotic areas are abolished lumbar sympathectomy is indicated. *Lumbar sympathectomy* has been successful when performed before ulcers develop. The *medical vasodilators*, Dibenzyline®, Priscoline®, Roniacol® and alcohol may be employed in combination with slight benefit. Maintaining a warm environment is essential In rare instances when ulceration proceeds to gangrene amputation is necessary (5).

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CHAPTER 42

Ergotism

ERGOTISM is a functional vascular disease associated with the intake of ergot or its derivatives.

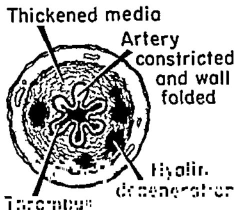
Etiology: Ergot itself (claviceps purpurea), ergotamine, ergotoxine or other ergot derivatives may be responsible for the disease. Ergot may be ingested inadvertently when it contaminates rye, wheat or other grains. The ergot in its natural state is contained in a deep purple fungus (St. Anthony's rust) which may attract attention because of its offensive odor. Ergot is employed therapeutically in obstetrics to produce uterine contraction, for the treatment of migraine to constrict cerebral arteries and for pruritis associated with jaundice. When contaminated bread is the cause the disease may occur in epidemics where the bread has been distributed. In some cases the disease has been produced by therapeutic doses of ergot (1), which suggests a sensitivity to the drug, while others have received thousands of injections of ergotamine tartrate without symptoms or signs of vascular disease. One patient with puerperal infection received 45 cc of ergotamine tartrate (22.5 mg) plus 24 cc of fluid extract of ergot in fourteen days and gangrene resulted (2). Another received 24 cc (12 mg) of ergotamine tartrate parenterally in seven days with loss of all the toes on one foot (3).

Pathology (figure 366): The media of the arteries is thickened and shows hyalin degeneration. The intima is folded and projects into the lumen of the vessel. Thrombi in the arteries, which may be undergoing various degrees of organization, are common. The vein wall is thickened.

History and Physical Examination: The presenting symptom often is burning pain in the extremities (St. Anthony's fire). In the early stages there is evidence of vasoconstriction of the pe-

ERGOTISM

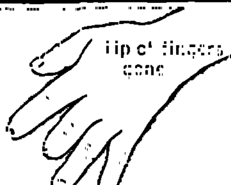
HISTORY OF INTAKE OF ERGOT
•
PARESTHESIAS
•
GANGRENE



SECTION OF ARTERY



RYE WITH ERGOT FUNGUS



GANGRENE OF HAND

Figure 366 Clinical and pathologic findings in patients with ergotism.

ripheral vessels. The pedal or radial pulses may be diminished or absent and the skin temperatures markedly decreased. Muscle cramps are common Frequently there is cyanosis and mottling of the tissues and late during the course of the disease cyanosis, paresthesias, coldness and bilateral gangrene of the fingers and toes, headaches, dizziness, weakness, nausea and vomiting may

occur. Visual disturbances, monoplegia or hemiplegia may occur if cerebral vessels are involved. Angina pectoris occurs when the coronary arteries are involved.

Pharmacology: One of the drugs that has produced ergotism is ergotamine tartrate which is widely used for the treatment of migraine. After injection there is a rise and then a fall in blood pressure and the pulse rate is slowed There is a decrease in the circulation in the hands, feet and digits. Early, constriction occurs which involves medium and small arteries, arterioles and capillaries. This may interrupt the circulation through the vasa vasorum, interfere with the nutrition of the vessel and produce intimal damage and arterial thrombosis (4).

Treatment: The source of the ergot is identified and removed. Vasodilators which have a direct action on the vessel wall, for example large doses of alcohol, Roniacol® and Priscoline® are employed. Anticoagulants are used to prevent vascular thrombosis.

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CHAPTER 43

Neurovascular Syndromes of the Upper Extremities

THESE CONSIST of the scalenus anticus, cervical rib, costoclavicular, hyperabduction, thoracic outlet, malposition and pectoralis minor syndromes.

SCALENUS ANTICUS SYNDROME

(NAFFZIGER SYNDROME)

This is a symptom complex consisting of pain in the hand, arm, shoulder, or neck with intermittent occlusion of the subclavian artery secondary to spasm or hypertrophy of the scalenous anticus muscle. The abnormality may be primary or secondary.

History: Adson and Coffey in 1927 called attention to the role of the scalenus anticus muscle in the production of pain in the arm (1). Ochsner, et al, in 1933 referred to several patients without cervical ribs who had relief of pain when the anterior scalenus muscle was severed (2) Naffziger in 1937 emphasized the importance of the anterior scalenus muscle in the production of the painful arm Naffziger and Grant described the scalenus anticus syndrome in detail in 1938 (3).

Anatomy: The scalenus anticus muscle originates from the transverse processes of the third, fourth, fifth and sixth cervical vertebrae and inserts on the scalene tubercle of the first rib (figure 367). The scalene triangle is formed by the anterior scalenus muscle anteriorly, the scalenus medius posteriorly and the first rib inferiorly. This serves as a sphincter through which pass the brachial plexus and the subclavian artery. The subclavian vein passes anterior to the scalenus anticus muscle and posterior to the clavicle (figure 373). The vein is situated so that pressure

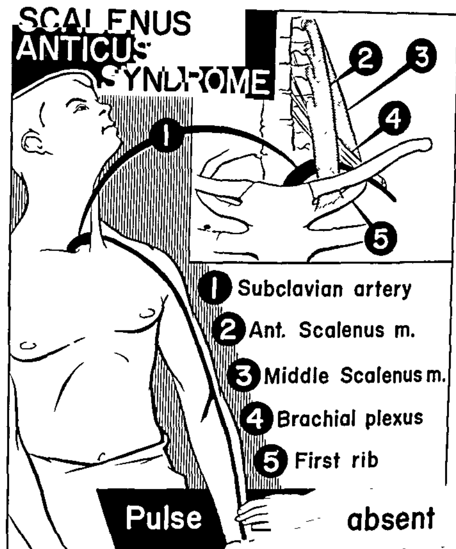


Figure 367 The scalenus anticus syndrome is diagnosed when elevating the head, holding the breath in inspiration and looking toward the side of the suspected lesion results in a diminished or absent radial pulse on the ipsilateral side, often with pain in the hand.

between these structures can produce venous obstruction. Sensory nerves pass under the tendinous origins of the scalenus anticus muscle from C4 to C7. The sympathetic nerve fibers run with the sensory nerves and surround the subclavian artery.

Etiology: The abnormality may be congenital or acquired.

Congenital Involvement Includes: A wide tendinous insertion of the scalenus anticus muscle on the scalene tubercle of the first rib which may produce pressure on the neurovascular structures of the neck. The scalenus anticus may fuse with the medius so that the neurovascular structures must perforate the muscle which results in irritation of the neurovascular structures.

Acquired Changes in the Muscle: These may result in hypertrophy, edema or spasm. Hypertrophy or edema occurs with unusual use of the arms and shoulders and occurs especially when changing from a sedentary to an active type of activity. This is seen also in wrestlers and weight lifters during their early training (4). Spasm of the anterior scalenus muscle is seen with poor posture, a low thoracic origin of the brachial plexus, a high first rib, an anomolous first rib, narrow thoracic outlet, or with a cervical rib. Spasm of the muscle may be secondary to cervical disc, pressure of the origins of the scalenus anticus muscle on sensory nerves, cervical arthritis, spinal cord tumors, tendonitis and other causes.

History and Physical Examination: Symptoms may be of nervous or motor origin. The nervous symptoms involve the sensory, motor and sympathetic nerves in well developed cases. The main sensory disturbance is pain. This involves usually the ulnar portion of the hand and arm and may involve the shoulder or neck as well. The pain may be sharp and lancinating and brought on by sudden rotation of the head, or by a forceful downward movement of the shoulders. At times the pain is dull, aching, burning or boring, especially toward the end of the day. The pain is felt over the distribution of the ulnar and median nerves. Muscular weakness of the hand may occur and may involve the thenar or hypothenar eminences, with wasting of the interosseous muscles. Numbness, paresthesias, hypesthesia and anesthesia may occur. Sympathetic stimulation may occur which produces a hand that is cool and cyanotic. Fullness in the region of the anterior scalenus muscle may be present. The muscle is often tense, enlarged and tender. Pressure over the involved side produces local tenderness, pain down the arm and into the hand. This is not present on the uninvolved side. An aneurysm of the

subclavian artery just distal to the obstruction produced by the scalenus anticus muscle occurs occasionally. A systolic murmur may be heard over the subclavian artery when it is partially occluded by the scalenus anticus muscle. A cervical rib may be present also and may be palpated in certain instances. The involved hand may be one or two degrees C colder than the control hand. If the patient is placed in a warm environment and the temperature of the fingers is measured, the involved hand warms more slowly than the control hand. Rarely, a causalgic type of pain with increased or decreased skin temperatures of the part may be present. When the part is warm, body cooling results in slower cooling of the diseased part than of the control. The grip may be poor because of muscle weakness Trophic changes occasionally are seen at the finger tips The deep reflexes are usually present but may be diminished or absent. The veins are distended if the hypertrophied muscle compresses the vein against the clavicle or if the vein is anomalous in its position and runs with the artery between the scalenus anticus and medius muscles. Sensory disturbances may be present especially over the ulnar nerve, which arises from the lower portion of the brachial plexus

The Adson Maneuver (figure 367): This may be positive and is carried out as follows (1). The patient sits in a chair with his arms at his sides. It is important to have the arms adducted as this places the scalenus anticus under tension while abduction of the arms relaxes this muscle. The radial pulse on the suspected side is felt by the observer. The patient elevates his chin, takes a big breath, holds it and looks to the side of the suspected lesion. The pulse diminishes or disappears with this procedure when the abnormality is present.

Diagnosis: Spasm, of the scalenus anticus muscle is diagnosed when the symptoms and signs of the disease are relieved within five minutes after procaine injection into the anterior scalenus muscle. The injection is made just posterior to the sternocleidomastoid muscle and is easily located by palpation if the patient elevates his chin, extends his neck and looks away from the side being injected. The spasm may be associated with intraspinal lesions, cervical arthritis, radiculitis of the fourth to seventh nerve roots, malignancy of the cervical spine, trauma of the shoulders,

or small thoracic outlet with nerve irritation due to dropping of the shoulder with nerve irritation as the nerve structures pass over the first rib (5). Nerve block does not relieve the pain when the scalenus anticus muscle is hypertrophied.

Special Procedures: X-rays should be taken of the cervical spine and first ribs to identify enlargement of the scalene tubercle, narrowing of the intervertebral foramina, long transverse processes of the lower cervical vertebrae, cervical rib, or anomalies of the first rib. The Adson maneuver should be carried out, employing the segmental plethysmograph so that objective evidence of altered arterial pulses with tension of the scalenous muscle may be demonstrated. Blood pressure differences in the two arms may be noted. When venous obstruction is suspected, a venogram will show the position of the venous obstruction. Also an increased volume of the limb can be demonstrated with the limb plethysmogram if veins are obstructed when the Adson maneuver is performed.

Differential Diagnosis: Other disease states producing pain in the arm should be ruled out before a diagnosis of anterior scalenus syndrome is made These include extensor tendonitis, brachial neuritis due to trauma, inflammation of the brachial plexus, lead poisoning, avitaminosis, trichinosis (6), cervical arthritis, cervical disc, neoplasm of the scalenus muscle, high first rib, hyperabduction syndrome, costoclavicular syndrome, arterial thrombosis or embolism, crutch pressure, polycythemia with arterial or venous involvement, arthritis of the intervertebral foramina, lipoma in the scalenus muscle, aneurysm of the subclavian artery, Raynaud's disease, thromboangiitis obliterans, subachromial bursitis, cervical disc, essential thrombophilia with increased coagulability of blood, arteriosclerotic obliterative disease, trauma from casts, and surgery.

Treatment: This may be medical or surgical; however, most patients are treated medically. As many of the cases are the result of acute trauma, supporative measures such as heat, salicylates and rest are adequate. Sleeping with the arms elevated, or in a narrow bed with the arms hanging over the side of the bed may provide relief. Weight reduction in obese patients may relieve pressure on the neurovascular structures. Surgical treat-

ment is carried out in those who do not respond to medical measures. Repeated procaine blocks should be tried before surgery is contemplated. Incision of the tendonous portion of the anterior scalenus muscle provides relief often by allowing the first rib to drop, thereby relieving pressure on the neurovascular structures. A sympathectomy may be carried out at the same time if the hand was previously cold or cyanotic. Removal of a cervical rib if present is carried out if it is apparent at the time of surgery that this is necessary to relieve symptoms. Section of the scalenus muscle may be necessary in those instances in which the vascular structures perforate the muscle. The anterior and middle scalene muscles may be severed to relieve pressure on the neurovascular structures.

CERVICAL RIB

This is a symptom complex characterized by pain in the hand, arm, shoulder and neck, secondary to ribs which are attached to the transverse processes of the lower cervical spine.

History: Cervical ribs were known to Vesalius and Galen. Willshire gave a clear description of the cervical rib syndrome in 1860 (1).

Sex, Age and Race: In one series females were affected more frequently than males, a ratio of 2 to 1. The disease is common in adults and all races are susceptible.

Etiology (figure 368): Cervical ribs are congenital in origin. Adson in 1947 found an incidence of 0.038 per cent in routine autopsies (7). Adson and Coffey found an incidence of 0.056 per cent among the general admissions to the Mayo Clinic (1). Between 55 and 85 per cent of the patients with cervical ribs have no symptoms. Signs of disease usually develop at adolescence or middle life at the height of muscular development. The disease is especially common in muscular individuals. Todd states that symptoms arise because of an abnormal shoulder girdle development (8). Normally the rectus abdominus muscles produce a descent of the sternum. An incomplete descent of the sternum or large descent of the shoulder tip results in stretching of the neurovascular structures (subclavian artery, brachial plexus and sympathetic nerves) over the cervical rib. Weakening of the suspen-

sory muscles of the shoulder, such as the trapezius, along with the weight of the arms causes descent of the shoulder tips. Jones attributes the neurological symptoms of cervical rib to abnormal development of the brachial plexus (9). If the brachial plexus originates mainly from the lower cervical or upper thoracic vertebral cord the peripheral nerves will overlie the cervical rib and produce symptoms. Pratt believes that overdevelopment of a normal first rib or abnormal development of the clavicle produces symptoms similar to that of a cervical rib (10). The symptoms may be of acute onset and are associated with unusual activity of the arms, head or neck. This is especially true in patients changing their occupation from a sedentary to an active one. The high incidence of right sided pain in the presence of bilateral cervical ribs is explained by the greater number of right handed individuals. Also the right brachial plexus is closer to the ribs than the left and thus is subject to pressure. Also the manner in which the scalenus anticus inserts into the scalene tubercle is important in producing symptoms. Symptoms are produced when the insertion is wide which narrows the scalene triangle. Patients who do not have symptoms often have narrow insertions of the anterior scalenus or it is implanted on the first rib more medially (toward the spine).

In many cases, a cervical rib produces irritation and spasm of the scalenus muscles which in turn traumatizes certain neurovascular structures of the neck. For this reason the cervical rib syndrome produces symptoms which are indistinguishable from those produced by hypertrophy, edema or spasm of the anterior scalenus muscles in the absence of a cervical rib Cervical ribs may vary greatly in their form, size and position (vide infra). When they are narrow and placed low in the neck (close to the first rib) symptoms may be absent. When they are wide and placed high in the neck direct irritation of the nerves and arteries may occur. The symptoms are unusually intense when the neurovascular structures are irritated directly by the abnormal rib as well as by spasm or hypertrophy of the scalenus anticus muscle. Fibrous bands between the transverse processes of the cervical vertebrae and first rib may simulate the cervical rib syndrome.

Sympathetic nerve fibers form a perivascular plexus around the

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In many cases, a cervical rib produces irritation and spasm of the scalenus muscles which in turn traumatizes certain neurovascular structures of the neck. For this reason the cervical rib syndrome produces symptoms which are indistinguishable from those produced by hypertrophy, edema or spasm of the anterior scalenus muscles in the absence of a cervical rib Cervical ribs may vary greatly in their form, size and position (vide infra). When they are narrow and placed low in the neck (close to the first rib) symptoms may be absent. When they are wide and placed high in the neck direct irritation of the nerves and arteries may occur. The symptoms are unusually intense when the neurovascular structures are irritated directly by the abnormal rib as well as by spasm or hypertrophy of the scalenus anticus muscle. Fibrous bands between the transverse processes of the cervical vertebrae and first rib may simulate the cervical rib syndrome

Sympathetic nerve fibers form a perivascular plexus around the

subclavian artery and supply the artery in its cervical portions. Sympathetic nerves run within the somatic nerves and in the brachial plexus and supply the major part of the arm and hand. The sympathetic fibers in this location often form a distinct and separate bundle in the inferior part of the nerve trunk that is nearest to the rib. Such a position exposes the sympathetic nerves to a greater risk of irritation or pressure than would be exerted on the motor or sensory fibers which may explain why patients occasionally have vasomotor disturbances without motor or sensory disturbances (11). Prolonged irritation of the nerves may produce spasm of the vasa vasorum causing degeneration of the subclavian artery with thrombosis and emboli.

Gruber (12) divided cervical ribs into four groups according to their extent of growth (figure 368). This has been modified as follows: 1) those which did not reach beyond the transverse process; 2) those which reached beyond the transverse process and have a free end; 3) those which are incomplete and connect with the first rib, and 4) those which are complete with a true cartilage which unites with the cartilage of the first rib. Symptoms are often caused by ribs which are of only intermediate length.

Usually the symptoms of cervical rib are referrable to nerve irritation and are the result of pressure on the nerves of the lowest trunk of the brachial plexus against bone or against a fibrous band extending forward from the end of the rib. The vascular disturbances are due often to irritation of the sympathetic fibers of the lowest trunk of the plexus. A brachial plexitis may occur. In most cases, however, it is evident that compression of the artery occurs because such compression of the arteries is observed at surgery. In addition, these patients exhibit disappearance of the radial pulse when the scalenus anticus muscle is put under tension with reappearance of the pulse when this muscle is relaxed.

Compression of the subclavian vein is not common with a cervical rib; however in the presence of an hypertrophied scalenus muscle or a deformed clavicle the vessel may be compressed between these structures.

History and Physical Examination: Symptoms are the result of irritation of sympathetic nerves, motor nerves and vascular

structures. Irritation of the sensory fibers results in pain felt along the inner side of the arm over the distribution of the internal cutaneous, ulnar and median nerves. But occasionally pain is felt over the distribution of the entire *brachial plexus*. The pain

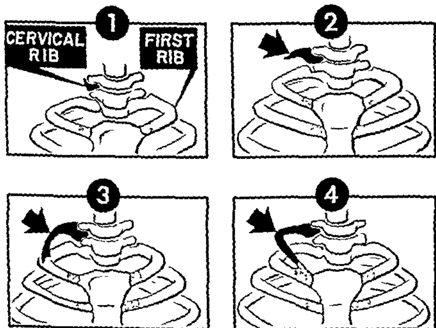


Figure 368. Four common types of cervical ribs.

may be associated with hyperesthesia, paresthesia or anesthesia (13). Pain is the principal symptom of a cervical rib and is usually referred to the shoulder, supraclavicular region, down the arm and the ulnar aspect of the forearm and hand and frequently to the

side of the neck and the ear (2). The pain may be mild and tingling or severe and lancinating. Supraclavicular tenderness is common. Pressure over the subclavian artery produces pain which radiates down the ulnar side of the arm to the little finger. The pain is aggravated by turning the head toward the affected side with the neck extended during deep inspiration (Adson maneuver). The pain follows activity such as sweeping or when changing activities from a sedentary to an active job which requires movement of the shoulders or neck.

Sympathetic Irritation: This results in coldness and hyperhidrosis of the fingers and hands. Slight cyanosis of the fingers may occur and the Raynaud's syndrome is encountered rarely.

Motor Weakness: This may occur with chronic irritation of motor nerves which is manifested by weakness and atrophy of the hypothenar or interosseous muscles (ulnar type).

Vascular Abnormalities: These may be a prominent part of the picture of a cervical rib. Intermittent occlusion of the subclavian artery occurs with tension of the scalenus muscle which, if prolonged as may occur with sleep, results in altered circulation to the arm. A systolic murmur is heard over the subclavian artery just before the radial pulse is obliterated. Aneurysm of the subclavian artery may result in local tenderness and swelling in the supraclavicular region and arterial thrombosis may occur from direct trauma to the artery or from sympathetic stimulation and spasm of the vasa vasorum (14, 15). Involvement of the sensory nerves may be detected by demonstrating analgesia with an esthesiometer or pinwheel and hypesthesia with the use of a brush or cotton. Changes in vibratory sense are uncommon but may be encountered Involvement of the sympathetic nervous system may be demonstrated by demonstrating the presence of hyperhidrosis with the Perspirometer or other appropriate instruments. Coldness of the arm or hand may be demonstrated with the thermistor thermometer especially if the environment is warm which promotes vasodilatation and the temperatures are compared on the normal and abnormal sides. Vascular change may be demonstrated by palpating a subclavian aneurysm in the supraclavicular fossa and by detecting a murmur stethoscopically. The Adson maneuver demonstrates the absence of the radial pulse with

the chin elevated, neck extended, the breath held in inspiration and the head turned to the affected side. Objective records of pulsations may be made with the limb plethysmograph. Permanent occlusion of the subclavian artery is demonstrated by low volume pulses from the limb with low pulse waves and low blood flow from the fingertip as compared to the normal side. These measurements are of particular value after vasodilatation with alcohol, heat or cervical sympathetic nerve block. Motor weakness is demonstrated with the dynamometer and a lower motor neuron lesion is detected with the electromyograph.

Diagnosis: This is made by x-ray examination of the neck which shows the presence of a cervical rib. The scalene tubercle is often enlarged. In addition there is plethysmographic evidence of arterial obstruction if the subclavian artery is thrombosed. Transient arterial obstruction is present when the Adson maneuver is carried out. Perspirometer tests show increased sweating.

Treatment: Medical treatment is indicated in most patients as many patients do not require surgery for this condition, especially if the symptoms are of sudden onset and are associated with unusual physical activity Rest, heat and salycilates are often sufficient. A reducing diet to increase the space in the scalene triangle and to decrease the drag on the shoulder girdle is advisable if the patient is obese. Sleeping with the hands above the head or sleeping prone on a narrow bed with the arms hanging may provide relief. Some of the symptoms may be relieved by repeated injections of the scalenus anticus muscle with procaine to allow lowering of the first rib (16, 17).

Surgical interruption of the tendonous insertion of the scalenus anticus muscle is sufficient to provide lowering of the first rib and provides relief of symptoms in most cases providing symptoms have not been present for long periods of time with irreversible changes in the brachial plexus. When there is pressure of the cervical rib on the brachial plexus with flattening of these nerve structures removal of the rib is necessary. Cervical sympathectomy in addition to this procedure is advisable if strong sympathetic vasoconstriction is demonstrated preoperatively by means of cervical sympathetic nerve blocks or other procedures (18).

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Treatment: Medical treatment is indicated in most patients as many patients do not require surgery for this condition, especially if the symptoms are of sudden onset and are associated with unusual physical activity. Rest, heat and salycilates are often sufficient. A reducing diet to increase the space in the scalene triangle and to decrease the drag on the shoulder girdle is advisable if the patient is obese. Sleeping with the hands above the head or sleeping prone on a narrow bed with the arms hanging may provide relief. Some of the symptoms may be relieved by repeated injections of the scalenus anticus muscle with procaine to allow lowering of the first rib (16, 17)

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COSTOCLAVICULAR SYNDROME

This is a symptom complex associated with pain in the arm and shoulder occurring as a result of pinching neurovascular structures between the clavicle and the first rib.

History: Falconer and Weddell described the costoclavicular syndrome which they observed in soldiers carrying heavy packs.

Etiology: Pressure on the brachial plexus which contains sensory, motor and sympathetic fibers and on the subclavian artery as a result of a pinching action between the calvicle and the first rib is the cause of the syndrome. It is produced by backward and downward displacement of the shoulders resulting in a scissors-like action which compresses these structures. Telford and Mottershead question the role of the clavicle in the production of the costoclavicular syndrome and state that pressure of the clavicle on the neurovascular structures is unusual in the presence of a normal thoracic outlet (19, 20).

History and Physical Examination: The symptoms are similar to those produced by the anterior scalenus syndrome or cervical rib syndrome. They are primarily neurogenic with pain being the predominant symptom. There is tenderness over the subclavian artery and brachial plexus with pain radiating into the arm and hand. Motor weakness occurs but is uncommon. Sympathetic irritation with coldness and sweating of the extremities is not an outstanding feature. Pain and circulatory disturbances of the hand due to arterial compression usually occur intermittently when the patient marches and carries a pack or when the shoulders are displaced backward and downward. The pain is relieved by throwing the shoulders forward or by elevation. If the ischemia to the hands is prolonged as follows long marches trophic changes and gangrene of the digits may occur.

Diagnosis (figure 369): There is usually a history of strain on the neck muscles producing displacement of the shoulders and obliteration of radial pulses. The symptoms are relieved and the pulse returns when the shoulders are forward and elevated. X-ray evidence of approximation of the clavicle and first rib and an abnormal plethysmographic record with the shoulders in the critical position are important diagnostic findings. A systolic

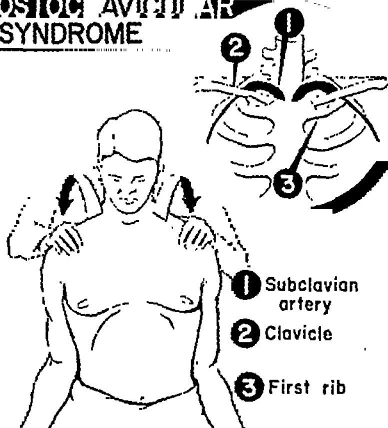


Figure 369. The costoclavicular syndrome is diagnosed by pulling the shoulders backward and downward obliterating the radial pulse.

murmur may be heard over the subclavian artery when the artery is partially compressed.

Treatment: Medical treatment is usually sufficient. Heat, rest and salycilates with the shoulders up and forward are helpful. A change in occupation may be necessary. Surgical treatment when necessary consists of removal of the first rib or clavicle.

HYPERABDUCTION SYNDROME

This is a symptom complex produced by hyperabduction of the arms, characterized by pain and diminution or obliteration of the

pulse with elevation of the arm when the arms are brought together above the head in the plane of the body.

History: Wright in 1945 and again in 1952 described the syndrome in detail (21, 22).

Etiology: The syndrome is produced by hyperabduction of the arms which produces stretching and ischemia of the brachial plexus. The important areas of irritation are: 1) the region in which the subclavian vessels and nerves of the brachial plexus pass between the clavicle and the first rib and 2) the area in which the vessels and nerves pass posterior to the pectoralis minor muscle beneath the coracoid process. The syndrome may result from prolonged sleeping in the supine position with the arms abducted. Occupational hyperabduction such as painting a ceiling or overhead working may produce the syndrome.

History and Physical Examination (figure 370): The neurologic symptoms consist of numbness and tingling in the tips of the fingers. The numbness may progress proximally and involve the ulnar side of the hand Vascular symptoms include coldness, hyperhidrosis, blanching and numbness of the hand. There is usually a history of a change in occupation which requires elevation of the hands. The tests for hyperabduction syndrome are positive. One test is as follows: With the patient either sitting or lying elevation of the arms in the plane of the body produces pain on the affected side which is associated with diminution or absence of the pulse (23). Recently this test has been modified by employing the plethysmograph Readings are taken at 0, 45, 90, 135 and 180 degrees with the body and variations in readings from side to side are observed or recorded.

Differential Diagnosis: The scalenus anticus maneuvers are generally negative; however they may be positive if there is secondary reflex spasm of this muscle. X-rays of the neck should be taken to rule out the presence of a cervical rib.

Treatment: This is usually medical. A change in occupation may be necessary. The arm should be kept in adduction. Heat, rest and salicylates may be administered. The sleeve of the gown or the pajamas may be pinned to the body of the garment or a two foot length of gauze may be tied around the wrist and to the side of the bed to prevent elevation of the arm during sleep.

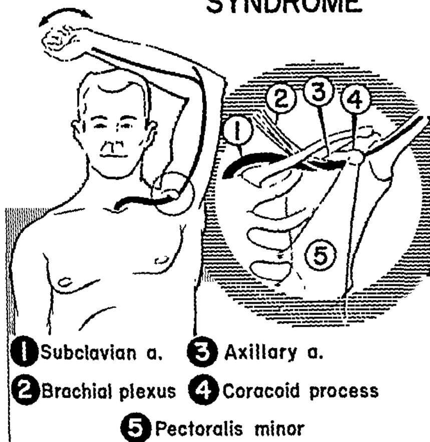


Figure 370. The hyperabduction syndrome is present when elevation of the arm results in obliteration of the radial pulse, often with pain in the hand. If the hand is exercised while elevated ischemia of the hand may develop.

Exercise to develop the elevator muscles of the shoulders (trapezius) may improve the patient by reducing the angle at which the structures pass under the coracoid process or between the first rib and scalenus anticus muscle. Surgical treatment is rarely carried out; however a portion of the first rib or clavicle could be removed to increase the size of the area through which the neurovascular

elements pass. The pectoralis minor and coracoid process could be treated surgically.

THORACIC OUTLET SYNDROME

Learmonth described various abnormalities of the upper rib cage structures and positions especially of the first rib and occasionally of the clavicle which produce symptoms of the arms similar to those of the cervical rib (24) (figure 371). Any of these abnormalities may produce irritation or compression of the subclavian vessels and nerves of the brachial plexus. The diagnosis is made primarily by ruling out the other syndromes of the upper extremities and by demonstrating radiologically the abnormalities of the rib cage and clavicle.

MAL POSITION SYNDROME

Pratt called attention to a neurovascular syndrome which follows *the abnormal positioning of the patient during surgery* (10). Here abnormal positions are maintained for long periods of time The lithotomy and other positions may produce kinking of the vessels. Leg straps and stirrups may damage neurovascular structures (figure 372).

PECTORALIS MINOR SYNDROME

A tight or hypertrophied pectoralis minor muscle could produce signs and symptoms by pressing on the neurovascular structures where they pass beneath this muscle. The diagnosis may be suspected when the shoulders are pulled up and back and symptoms are produced in the arms with diminished radial pulse. A systolic murmur which is loudest near the coracoid process occurring with partial compression of the artery is significant (figure 373).

MEDICAL-LEGAL ASPECTS OF THE NEUROVASCULAR SYNDROMES OF THE UPPER EXTREMITIES

It is often necessary to determine if the patient's occupation is an exciting cause of pain in the arm. This question may arise in *the presence of such abnormalities as a cervical rib*. The question is especially difficult if acute arterial thrombosis occurs in patients

THORACIC OUTLET
SYNDROME

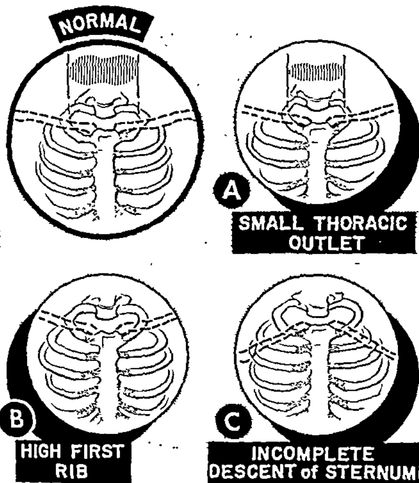


Figure 371. Abnormalities of the thoracic outlet which may produce neuritic or circulatory disturbances in the hand.

with a cervical rib. Acute arterial thrombosis in patients with a cervical rib is probably related to injury by the rib if the thrombosis occurs within a week of unusual activity which could serve as an exciting cause. The hyperabduction syndrome or other neurovascular syndromes of the upper extremities could be caused

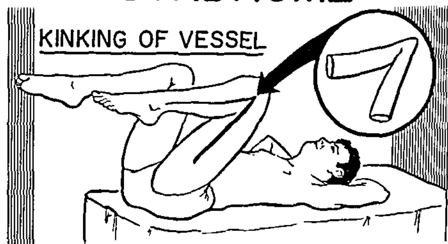


Figure 372 Abnormal positions of the limbs resulting in kinking of blood vessels or pressure on nerves may result in neurovascular disturbances. Unusual positions are sometimes employed during surgery.

by the occupation if symptoms develop within a week of change of occupation which could serve as an aggravating cause. If others are performing a similar type of work without symptoms and there is no recent change in the patient's activities the symptoms would be considered unrelated to the occupation.

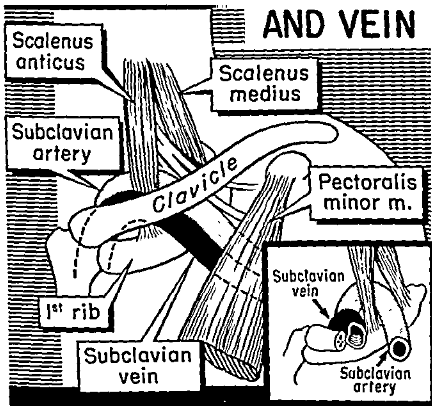


Figure 373. The subclavian artery is behind the anterior scalenus muscle. The subclavian vein is in front of this muscle. Both artery and vein run under the pectoralis minor muscle and may be traumatized if this muscle becomes hypertrophied.

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Figure 374. Silas Weir Mitchell, 1830 to 1914. He described causalgia and erythermalgia. He devoted much of his time to experimental work related to neurology and the neurovascular diseases.

CHAPTER 44

Post Traumatic Syndromes

THIS CHAPTER contains a discussion of major causalgia, minor causalgia and Sudeck's atrophy. Causalgia is a post-traumatic state involving peripheral nerve injury which is associated with vasomotor disturbances. Sudeck's atrophy is a post-traumatic state associated with decalcification of bone.

Anatomy and Physiology of Peripheral Nerves: The post traumatic syndromes often are associated with peripheral nerve injuries. A peripheral nerve consists of: 1) afferent nerve fibers which have sensory functions, and 2) efferent nerve fibers which have motor and autonomic functions, this latter having vasomotor, pilomotor and sudomotor activities. The vasomotor nerves are for the most part small unmyelinated nerve fibers which are scattered throughout the nerve trunk. The median and posterior tibial nerves contain many vasomotor fibers while the radial and external popliteal nerves contain few such fibers. Therefore, median or posterior tibial nerve damage or division produces marked changes in digital circulation while little change results from damage or division of the radial or external popliteal nerves. Usually immediately after division of a peripheral nerve there is a sympathectomy-like effect with vasodilatation, increased warmth of the part and lack of vasomotor reactions; while irritation of a peripheral nerve results in vasoconstriction. In general, the distribution of the vasomotor nerves to the periphery is similar to that of the sensory distribution; therefore, immediately after division of the nerve areas of analgesia also demonstrate increased warmth. Following division of a peripheral nerve there are two phases which may be observed. The first is that of vasodilatation with increased warmth of the part due to interruption of the sympathetic vasoconstrictor fibers to the blood vessels. The second is

a vasoconstrictive phase which is not neurogenic in origin as vasodilatation cannot be produced by a nerve block, but may be due to degeneration of the sensory fibers with consequent loss of vasodilatation (the axone reflex) or to an increased sensitivity which the severed postganglionic nerves show to adrenalin. A digit which is completely denervated will not respond reflexly to changes in body temperature but will respond to the local metabolic needs of the tissues as may be demonstrated by the reactive hyperemia test. A digit, however, which is incompletely denervated may show almost normal reflex vasomotor activity when only a part of the vasomotor nerves are injured. In general, vasomotor and sensory functions are lost together; however vasomotor and motor functions, of the hand at least, may be lost separately.

Types of Peripheral Nerve Injuries: Nerve injuries are classified as complete or incomplete (1). In the first group there are clinical manifestations and loss of function. In the second group there may or may not be loss of function or abnormal reactions. Evaluation of the functions of the digits of the upper or lower extremity is carried out by examining: 1) the motor system by observing active movement of the part and by the electromyogram; 2) the sensory system, especially touch and pain, and 3) the autonomic functions including the sweat pattern and vasomotor activity. Sweat reactions can be tested conveniently with the Perspirometer or psychogalvanometer. Vasomotor tests are made with the skin thermometer and plethysmograph. The circulation is studied with the patient at rest, with reflex body heating and reflex cooling and with direct digital heating and cooling. Vasomotor responses of the digits also are elicited by externally induced stimuli, such as inspiration, tickle and pain. Normally there are no significant differences between the vasomotor reactions of the upper and lower extremities. It is important in evaluating the peripheral circulation to place the thermistor sensing element or plethysmographic cup properly. Lesions of the ulnar nerve may be detected with the detectors on the little finger, the median nerve from the index finger and the radial nerve from the thumb. Because of overlapping of vasomotor nerves, complete abolition of reflexes as measured from a digit may not

take place by complete division of one nerve. Complete damage of the brachial plexus produces loss of sensation below the shoulder and no vasomotor responses occur in the fingers. The toes are innervated for the most part on the dorsal aspect by the peroneal nerves and on the volar aspect by the tibial nerves. As the sciatic trunk gives rise to these two nerves, division of the sciatic nerve produces changes in both areas.

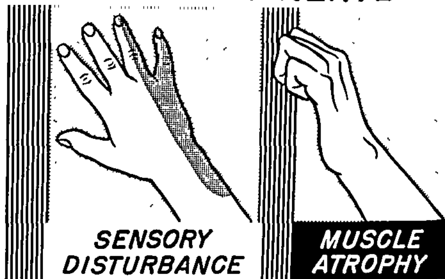
Complete Nerve Lesions: *Division of Ulnar Nerves* (figure 375): A sensory disturbance is observed in the fourth and fifth fingers. Motor weakness is revealed by interosseous atrophy and atrophy of the hypothenar eminence. The temperature of the fifth finger early in the course of the disease is higher than its companion finger. Body cooling followed by body heating produces no significant change in the temperature of the abnormal fifth finger; however temperature changes occur in the fifth finger of the normal hand. Later, during the constricted phase of the disease the temperature of the abnormal finger at a comfortable room temperature is below the companion finger and the vasomotor reactions to indirect heat and cold are abnormal.

Division of Median Nerve: There is sensory loss on the tips of the second (index) and third fingers and in the palm of the hand. Motor loss is seen as an inability to make a fist. Sweating is decreased over the palm and tips of the second and third fingers. In the dilated stage the tip of the second finger is warmer than that of the normal hand With body cooling and heating there is minimal vasomotor change in the second finger with the damaged nerve as compared with a normal finger. The inspiratory reflex is absent in the second finger with the damaged nerve but is present in the fifth finger and other fingers with normal innervation.

Division of Radial Nerve: Sensory loss is at the base of the thumb. Motor function when lost is shown by weakness of the thumb. The temperature of the thumb during the dilated stage is warm and the vasomotor reactions are absent.

Division of the Posterior Tibial Nerves: There is analgesia and anesthesia of the plantar surface of the foot. There is no apparent motor dysfunction and no sweating on the plantar surface of the foot. The temperature may be high or low depending on the

COMPLETE INTERRUPTION OF ULNAR NERVE



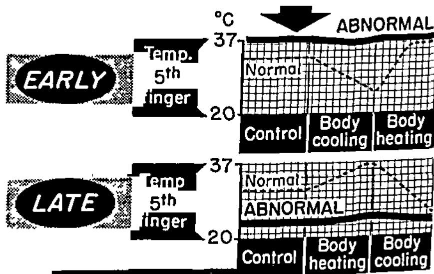


Figure 375 The effect of complete and incomplete division of the ulnar nerve on sensory, motor and vasomotor activity.

amount of time which has passed since the nerve was severed. Body heating and cooling produce no vasomotor changes of the toes.

Division of the Sciatic Nerve: The branches of the sciatic nerve are the peroneal (common, superficial and deep), anterior and posterior tibial and sural. Division of the sciatic nerve results in: 1) a sensory disturbance on the plantar and dorsal surface of the foot and lower portion of the leg, 2) motor weakness of the foot; 3) absence of sweating over the area of analgesia, and 4) absent vasomotor reflexes.

Division of the Common Peroneal Nerve: The branches of this nerve are the lateral sural cutaneous and the deep and superficial peroneal. Division of the common peroneal nerve results in sensory loss over the lateral and anterior surface of the foot. The motor defect results in an inability to evert the foot. There is dryness over the anesthetic areas.

Incomplete Nerve Lesions: The effects are similar in their distribution to complete nerve lesions, however because of overlapping of nerves evidence of damage may not be revealed by vasomotor tests. Incomplete nerve lesions often result in: 1) major causalgia; 2) minor causalgia, or 3) Sudeck's atrophy.

MAJOR CAUSALGIA

This is a post-traumatic syndrome consisting of the triad of burning pain, autonomic dysfunction and trophic changes. The syndrome follows wounds which are associated with peripheral nerve injury. The syndrome occurs often as a result of penetrating war wounds.

History: The term causalgia means "burning pain" and was employed by Silas Weir Mitchel The syndrome was first described in an excellent publication by Mitchel, Morehouse, and Keen (2). Dr. Mitchel lived between 1830 and 1914 and was one of the most accomplished and versatile physicians of his time. As a young man he took first place among the physiologists. As a middle aged man he was first among the physicians and as an elderly man he was first among the novelists of his country. Of significance are the follow-up studies on the cases described by him made by

J. K. Mitchel and published under the title "Remote Consequences of Injuries of Nerves and Their Treatment" (3).

Age, Sex and Race: All ages, sexes and races may be affected.

Etiology: Causalgia is common when nerve injury is incomplete and is rare with complete nerve injury as after an amputation (4). Various theories have been suggested. 1) Leriche suggested that painful irritation of sensory nerves results in afferent impulses which bombard the vasomotor center (figure 376). This results in increased sympathetic activity prompted by the efferent impulses which reach the vessels, sweat glands and erector pili muscles. The vascular response is modified by the amount of injury to the peripheral sympathetic nerve trunks. If the injury is great, vasodilatation results and if slight vasoconstriction occurs (5). 2) Stimulation of afferent sympathetic nerve fibers has been suggested as a cause (6, 7) (figure 377). If this occurred one could explain the relief of pain which frequently follows sympathectomy. However, to date, there is no anatomic evidence of such fibers in the peripheral nerves. In fact, there is strong evidence against this type of sympathetic nerve activity. 3) Livingston (7) has proposed the theory of the internuncial pool which postulates that an irritative focus in the extremity resulting from trauma produces afferent impulses traveling over sensory nerves to the spinal cord where a zone of irritation is produced (figure 378). The irritated cord in turn stimulates lateral and anterior horn cells which produce abnormal motor and vascular responses This theory is intriguing but is without objective proof. 4) Doupe, Cullen and Chance (8) suggested that the pain was due to an alteration in the excitability of sensory nerves brought about by sympathetic nerve activity which occurs as a result of emotional stress, thermoregulation and other stimuli (figure 379). This theory is supported by the rather constant relief of pain afforded by sympathetic block. 5) The possibility of vasodilatation produced by an axone reflex of the sensory nerves was pointed out by Kuntz (9).

History and Physical Examination: Usually there is evidence of a penetrating wound in the region of the median and sciatic nerves. Burning pain is present distal to the site of the injury. The pain appears immediately or after a few weeks after injury

and is associated with hyperesthesia. Partial relief from pain is obtained sometimes by placing the arm in lukewarm water or covering it with a cloth. Light touch or cold drafts of air may produce paroxysms of pain. The application of moisture seems to

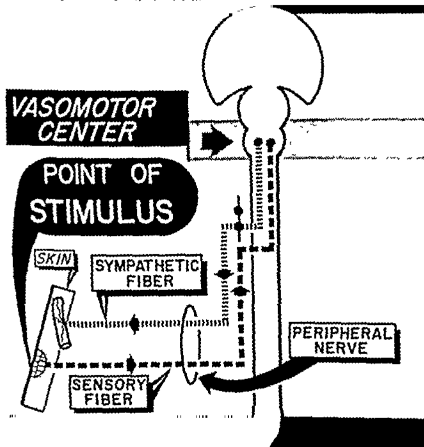


Figure 376. Etiology of causalgia; theory of Leriche.

provide relief (4, 10). The autonomic dysfunction may cause vasodilatation (early) (11), or vasoconstriction (late). The part may be dry (early) or exhibit hyperhidrosis (late). Trophic changes such as scaling of the skin are common. Ridges of the

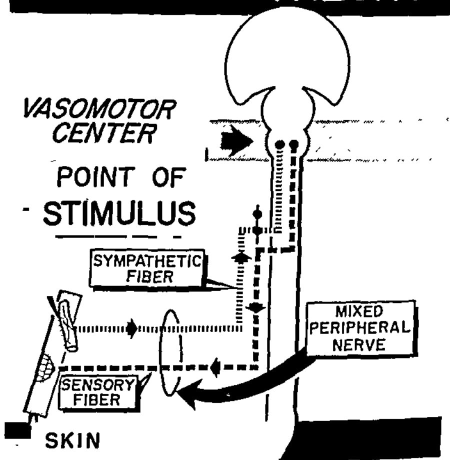


Figure 377. Etiology of causalgia; afferent sympathetic impulse theory.

nails and atrophy of the hair of the extremity may occur (figure 380). Often patients with warm extremities prefer cool, moist applications while those with cool extremities prefer warm moist applications. Stiffness of the joints is not uncommon (4). Motor

paralysis is evident with complete division of the nerve. Sensory changes, which may or may not follow a peripheral nerve distribution, usually can be detected.

Diagnosis: This is based on the history of trauma and evidence

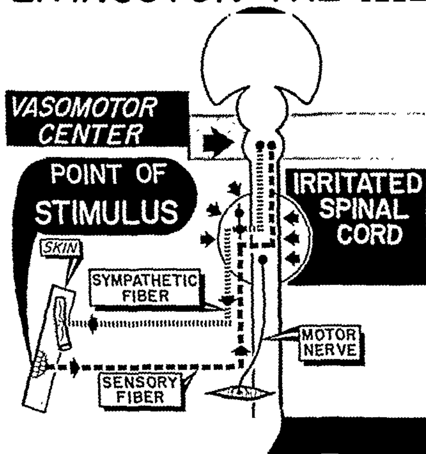


Figure 378. Etiology of causalgia; theory of Livingston.

of a nerve lesion as revealed by motor weakness, sensory change, vasomotor disturbances and trophic changes. An abnormal electromyogram or the reaction of degeneration using electric methods is helpful. The presence of pain of a burning type which spreads

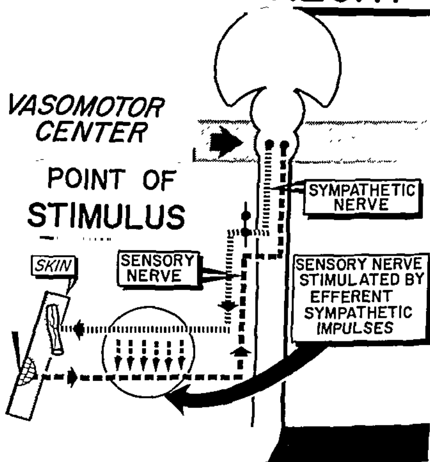


Figure 379. Etiology of causalgia, theory of Doupe, Cullen and Chance.

beyond the site of the lesion is characteristic. A warm or cool extremity with hyperhidrosis and trophic changes may be seen. The vasomotor disturbances can be revealed by plethysmographic and thermometric tests. The temperature variation test is of particular value and shows abnormal vasomotor reactions. Sweat measurements also are of importance.

Treatment: This should include the following: 1) The patient should be reassured. 2) Moist compresses should be applied if relief is obtained. The compresses should be warm if the extremity is cool and cool if the extremity is warm. 3) The part should be wrapped to protect it from drafts. 4) Opiates should be used sparingly because of the possibility of addiction 5) Procaine sympathetic blocks into the stellate and first thoracic ganglia or

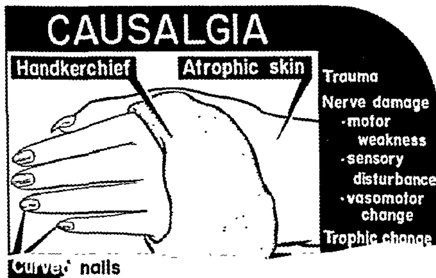


Figure 380 A damp handkerchief frequently provides symptomatic relief

into the second lumbar ganglion give transient relief and this procedure may be repeated periodically (4, 7, 11, 12). If after two or three injections transient relief is obtained repeatedly a sympathectomy is advisable 6) Gangloinic blocking agents such as mecamylamine (Inversine®) and Ecolid® might give some measure of improvement 4, 13, 14) 7) Local injection into trigger zones and below and above these sites may be tried 8) A surgical ganglionectomy usually is the treatment of choice. The following have been successful in isolated cases: 1) periarterial sympathectomy (5), 2) removal of an irritating focus such as a thrombosed artery or vein, 3) section and resuture of a nerve (10); 4) rhizotomy, and 5) cordotomy.

MINOR CAUSALGIA

This is a post-traumatic state which is associated with injury to tissues and is associated with pain, hyperesthesia and vasomotor disturbances. There is no obvious involvement of large nerves as occurs with major causalgia. The disease has been referred to as atypical causalgia, reflex dystrophy, post-traumatic spreading neuralgia, sympathalgia, irritative nerve lesions, post-traumatic pain syndrome, traumatic angiospasm, chronic traumatic edema, reflex nervous atrophy and peripheral acute trophoneurosis.

History: The disease was first described by John Homans (15) under the name of minor causalgia who differentiated minor causalgia from major causalgia because of the observation that the disease could occur without evident injury to peripheral nerve trunks. He described six cases only one of which was associated with involvement of a large (median) nerve. The other five showed no demonstrable nerve damage and were associated with arterial embolism, puncture wounds not involving nerve trunks, thrombophlebitis, fracture and felon of the thumb.

Etiology: The mechanisms producing pain and vasomotor disturbances are not known; however it is likely that in some cases damaged tissues produce some irritation of sensory nerves. The impulses may enter the spinal cord by the posterior root and ascend to the vasomotor center which results in sympathetic nerve irritation and results in vasoconstriction and sweating If sympathetic nerve fibers have been damaged along with the sensory nerves, a local sympathectomy may result in vasodilatation which is followed later by vasoconstriction. This theory is supported by the observations that: 1) removal of an irritative focus surgically, for example removal of a thrombosed artery; 2) blocking of afferent sensory nerves by novocaine; 3) cutting the posterior roots; 4) sympathetic ganglionectomy, or 5) periarterial sympathectomy have in isolated instances produced improvement.

Age, Sex and Race: All ages and races and both sexes are susceptible.

History and Physical Examination: After trauma from a blunt or sharp object, infection, frost bite, burn, arterial embolus or thrombophlebitis there follows a vasomotor disturbance charac-

terized usually by vasodilatation with increased warmth of the part below the traumatized area to be followed in weeks or months by vasoconstriction with increased sweating. Trophic changes such as thinning and discoloration of the skin with or without scaling may be present. Non-pitting edema is common. There is hyperalgesia, the skin being sensitive to drafts and to changes in environmental temperature and to pressure. There may be glove-like hyperesthesia which does not follow a sensory nerve distribution. The muscles are first hypertonic, then later often atonic, Weeping eczema may appear. The nails become brittle and ribbed. The disease is commonly associated with psychoneurotic disturbances which occur either prior to or after the trauma.

Diagnosis: This is based upon a history of trauma followed by vasomotor disturbances and hyperesthesia. A trigger zone may be present which when touched results in severe pain. Vascular studies of the large arteries early reveal increased pulsations of digits with later a decrease. The minute vessels show a diminished response to cold and the hyperemic reaction to cold (see cold test) is much slower than normal. Plethysmograms and skin temperatures reveal the presence of vasodilatation or vasoconstriction as compared with the normal companion limb The temperature variation test (cold-hot test) reveals differences in vasomotor reactions in the diseased as compared to the normal limbs.

Differential Diagnosis: Minor causalgia is to be differentiated from 1) major causalgia and 2) Sudeck's atrophy. The former shows evidence of nerve trunk involvement and the latter shows evidence of bone involvement.

Treatment: Physiotherapy in the form of heat and active and passive movement should be encouraged. When vasoconstriction is present ganglionic blocking agents such as Inversine® and sympathetic blocking agents such as Priscoline® along with vasodilating agents such as alcohol and Roniacol® should be employed. Local painful zones (trigger zones) may be injected with procaine below, at and above the trigger zone. A sympathetic ganglion block with novocaine often produces dramatic temporary relief. If relief is obtained a surgical sympathectomy is indicated (16). When pain is severe amputation has been performed; however relief of pain is not consistent with this procedure.

SUDECK'S ATROPHY

Sudeck's atrophy, often called painful osteoporosis and reflex sympathetic dystrophy with osteoporosis, may be defined as a painful condition of an extremity following trauma which is associated with tenderness, edema, hyperhidrosis vasomotor disturbances with x-ray evidence of osteoporosis in the region of, or distal to, the injury.

History: The disease was first described by Sudeck in 1900 (17) and the x-ray findings were described in detail by Kienbock in 1901 (18).

Age, Sex and Race: All ages and races and both sexes are susceptible.

Etiology: This is thought to be due to a vasomotor disturbance of the vessels innervating bone. It has been suggested that 1) the osteoporosis is the direct result of trauma and is brought about by reflex action through the vascular system; 2) it is secondary to disuse; 3) it is a normal process of bone regeneration and is a physiologic reaction to trauma (19).

History and Physical Examination: Pain occurs soon after injury which may be of minor or severe degree. The osteoporosis may have its onset as early as a week after injury and may or may not improve as the clinical symptoms subside. The vasomotor disturbances may consist of vasodilatation or vasoconstriction depending upon the stage of the disease. Often vasodilatation occurs early and vasoconstriction later. The Raynaud's phenomenon may be present. The skin is often tender, moist and cyanotic and stasis edema may be present. Commonly the site of injury is the wrist or ankle. The pain is aggravated by exercise and may be progressive over a period of weeks. Stiffness of the joints often prevents movement of the part.

Laboratory Studies: X-rays show typical changes in bone. Vasomotor disturbances may be detected by comparing the temperature with that of the companion extremity and by vascular study. The temperature variation (cold-hot) test is of particular value.

Diagnosis: The diagnosis is based upon the history of trauma followed by vasomotor disturbances and osteoporosis. Osteoporo-

sis appears early and is spotty early and diffuse later and is distal to the site of the injury (figure 209).

Differential Diagnosis: One should differentiate myositis, tenosynovitis and central nervous system disease such as syringomyelia and myelodysplasia. The osteoporosis of Sudeck's atrophy may be differentiated from that due to disuse by its early appearance after the injury in the former. One should differentiate anxiety neuroses, malignancy, osteomyelitis, arthritis, gout, flat feet, cellulitis, lymphatic or venous edema.

Treatment: Physiotherapy in the form of heat, massage and active exercise should be encouraged. This may be carried out after sedation or analgesics if necessary. During the vasoconstrictive phase of the disease vasodilating drugs, such as Priscoline®, alcohol and Roniacol® should be employed. Hot, moist packs may be beneficial. A cervical or lumbar sympathetic procaine block should be carried out to determine its effect on the vasomotor tone, on pain and on mobility. If satisfactory results are obtained a surgical sympathectomy could be performed; however results with this procedure have been irregular. Sympathectomy should not be performed for the osteoporosis alone as clinical improvement often occurs but the osteoporosis may remain unchanged.

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CHAPTER 45

Erythermalgia

ERYTHROMELALGIA

ERYTHERMALGIA is a functional vascular disease characterized by attacks of burning pain occurring in red extremities when the skin temperature is above a critical level.

History: The disease was first described by Silas Weir Mitchel who noted the relationship between the red color of the skin, pain and swelling of the acral portions of the body (1).

Etiology: The disease has been attributed to 1) heat sensitivity of the skin, 2) loss of vasomotor control and 3) disease of the sympathetic nervous system. It has been suggested that the abnormality results from an increased susceptibility of the skin to a warm environment since the attacks can be reproduced if the skin temperature is raised to a critical level which is usually greater than 31 degrees C The symptoms are reported to occur when the skin temperature is elevated even if the blood flow to the extremity is completely obliterated by a tourniquet. Silas Weir Mitchel felt that the basic abnormality was a vasomotor neurosis in which the control of normal vasomotion is lost, the vessels at times being overly constricted and at other times overly dilated. Buerger felt that the basic disease process resided in the sympathetic nervous system (2).

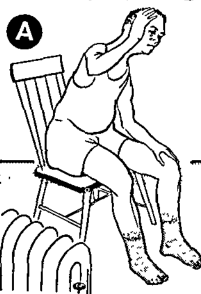
Classification: The disease may be *primary* or *secondary*. In its primary form no underlying disease is present. Secondary erythermalgia may be associated with arteriosclerosis, hypertension, peripheral neuritis, frost bite, immersion foot, trench foot, polycythemia, disseminated sclerosis, infectious diseases, hemiplegia, chronic heavy metal poisoning, gout or other abnormalities.

History and Physical Examination: The patient complains of aching, throbbing, burning or itching of the feet or hands, when

the skin temperature is warm. The pain is common in the feet but the hands may be involved also. The attacks are more common in the summer than in the winter and are associated with redness and swelling of the part. Initially the attacks are of short duration but as the disease progresses the duration in-

ERYTHERMALGIA

PAIN



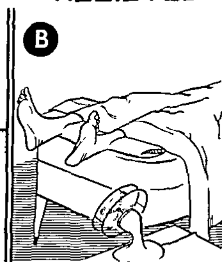


Figure 381. Clinical findings in patients with erythermalgia

creases. The pain may be severe and interfere with sleep. The process is bilateral and often involves the weight bearing surfaces. The attacks are aggravated by local heat, dependency, local friction and exercise and are relieved by elevation and a

cool environment (figure 381). Systemic symptoms may be present. Palpitation, vertigo, headache, hyperhidrosis and trophic lesions of the skin and nails have been described. Raynaud's phenomenon may be present (3).

Age and Sex: Men are affected more frequently than women. The middle age group is usually involved, however children have been affected. The disease may occur in families.

Diagnosis: The diagnosis is made by raising the skin temperature to 31–36 degrees C and demonstrating the association of the

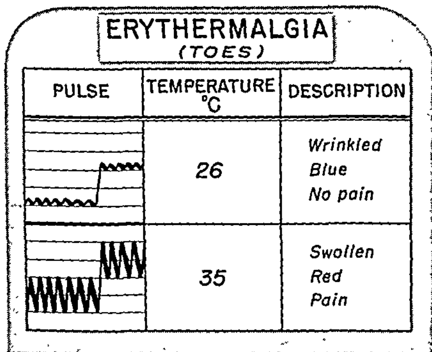


Figure 382. Correlation of pulsations, skin temperatures, appearance of toes and symptoms. When the pulses are small and the temperature cool the toes often are wrinkled and blue, and there is no pain. If the pulsations are tall and the skin temperature high the digits often are swollen, red and painful.

burning sensation of the digits with warm skin temperatures (4) (figure 382). Usually the direct application of dry heat is more disturbing than wet heat. The disease often can be reproduced by putting an electric pad on the trunk to provide body

heating. A thermistor thermometer attached to a finger makes it possible to correlate skin temperature and symptoms. A plethysmographic cup attached to a digit may record unusually large digital pulsations which are associated with a warm skin temperature, swelling, redness and pain (figure 382). Elevation of the limbs results in the persistence of redness; however there is some decrease in pain. Dependency of the limb results in intensified burning pain and swelling. Exercise likewise results in burning of the skin. Routine vascular study shows no organic vascular disease; however increased pulsations are present after body heating and whiskey.

Differential Diagnosis: The organic occlusive arterial diseases must be differentiated from erythermalgia. The former is characterized by a decrease in the peripheral pulses, elevational pallor, dependent rubor and intermittent claudication. Neuritis, pernio and frostbite should be differentiated also.

Treatment: Drugs producing vasoconstriction may be helpful, for example ergotamine tartrate (Gynergin®), tobacco and ephedrine (5), antihistamines and prednisone may prevent swelling. Dibenzyline® dries the part if hyperhidrosis is present (6). Desensitization to heat should be tried by placing the part in water 28 degrees C, two to three minutes a day for three to four days and gradually increasing the temperature. Aspirin relieves pain but not the swelling (3). Sympathectomy dries the part but swelling may be intensified.

Prognosis: The symptoms usually are recurrent at irregular intervals. The outlook as to life is excellent.

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Figure 383 Giovanni Battista Ca [illegible]
describe valves in the major veins [illegible]
the anatomists of the middle ages [illegible]
thinking of the medical profession regarding the circulation He was one of the greatest figures in the early history of modern anatomy.

CHAPTER 46

Diseases of the Veins

This chapter contains a discussion of: 1) the physical examination relative to the veins; 2) the diseases of the veins.

PHYSICAL EXAMINATION

The patient should be observed in the supine and standing positions to observe and palpate the veins in their distended and nondistended states. The long saphenous, short saphenous, femoral veins and veins of the upper extremities should be examined. The long saphenous vein is located on the inner aspect of the calf and thigh The short saphenous is located on the posterior aspect of the calf running from heel to popliteal space. The femoral vein is located just below the inguinal ligament. The veins of the neck, chest, arms and hands should be observed.

THE COMMON SIGNS OF VENOUS DISEASE: These are edema, ulcers, stasis dermatitis, prominent veins, increased temperature of vein, abnormal venous collateral patterns and calcification of tissues.

Edema: *This is characteristic of venous obstruction* and venous insufficiency. Acute venous obstruction (thrombophlebitis) results in a tense pitting edema which is reduced somewhat by elevation of the limb The limb may be hot when an acute inflammatory process is present or may be cool if secondary arteriolar constriction has occurred With chronic phlebitis the edema may be replaced by a hard, fibrotic, non-pitting edema.

Ulcers: These are common with chronic venous obstruction and venous insufficiency. Characteristically they are present on the inner aspect of the ankle just above the malleolus.

Stasis Dermatitis: Often the skin on the inner, lower third of the ankle is discolored brown with many dilated vessels. This is

due probably to chronic capillary venular hypertension (figure 295).

Prominent Veins: These are characteristic of varicose veins but may be caused by arteriovenous fistulas.

Veins with Increased Temperature: Arteriovenous fistulas are a common cause for this abnormality. This is especially true when varicose veins occur in the young. Hot veins occur also with acute phlebitis or when periphlebitis is present.

Abnormal Venous Patterns (figure 279, 280, 281): The location of prominent superficial veins may suggest the presence and location of venous obstruction. Numerous veins around the neck which are bilateral suggest obstruction of the superior vena cava. Numerous veins around one shoulder suggest subclavian vein obstruction. Numerous veins bilaterally distributed over the lower portion of the abdomen suggest obstruction of the inferior vena cava. Prominent veins below the knee suggest disease of the popliteal, short saphenous or communicating veins.

Calcification: Calcification of soft tissues or veins may occur with chronic venous obstruction and may be present in the post phlebitic leg (figure 207).

TESTS FOR VENOUS DISEASE: These are important to detect venous obstruction or insufficiency and include the following: 1) percussion test; 2) Brodie-Trendelenburg test; 3) Perthes test; 4) Ochsner and Mahorner test; 5) Pratt test, and 6) venous pressure tests.

Percussion Test (figure 384): This test is employed for examining the superficial veins and will be described for the long saphenous (1). The fingers of one hand are placed on the vein below the knee and the vein is percussed with the hand above the knee. The pulse wave is transmitted to the lower palpating hand if the superficial valves are incompetent but not if they are competent. The test depends upon the principle that competent valves can interrupt the transmission of a pulse wave through a column of blood The technique is useful when superficial veins are not visible.

Brodie-Trendelenburg Test (figure 385): This test is employed to determine the competency of the saphenofemoral and communicating valves (2, 3) The technique is as follows: Part A:

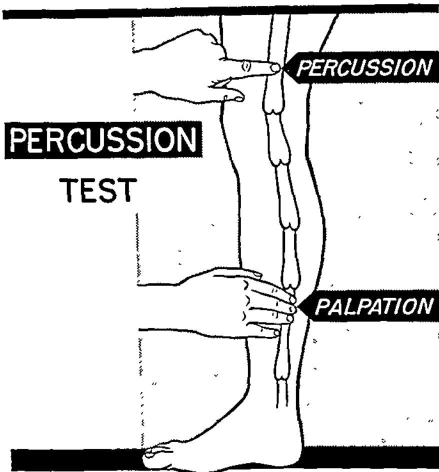


Figure 384. Percussion test for determining valvular insufficiency. The vein is palpated with the right hand in the region of the calf. The vein is percussed with the left hand in the region of the thigh. An impulse will be felt with the right hand if the valves are insufficient

The leg is elevated vertically and the veins are emptied by stroking the vein toward the heart. A tourniquet measuring $^3/_8$ inch in diameter is applied to the upper part of the thigh to occlude the superficial veins which are occluded easily. The patient stands and the time required for filling of the veins distal to the tourniquet is noted. The tourniquet is removed after thirty-five to sixty seconds. Part B: The test is repeated but this time the

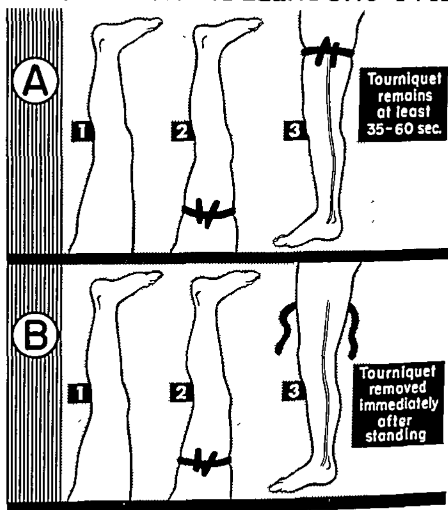


Figure 385. Brodie-Trendelenburg test. Part A. 1) Leg elevated, 2) a tourniquet is applied; 3) the patient stands. Part B 1) the leg is elevated, 2) a tourniquet is applied; 3) the tourniquet is removed immediately after standing (see text for explanation).

tourniquet is removed quickly and the direction of flow and time of venous filling is noted.

Normal Reactions: The superficial veins fill after thirty-five seconds whether or not the tourniquet has been applied because

blood fills the veins from below by way of the arterial circulation. This indicates competency of the valves of the great saphenous and of the perforating veins. When the tourniquet is removed quickly the veins fill slowly after thirty-five seconds.

ABNORMAL REACTIONS: These have been termed positive, negative and double positive.

Positive: (Incompetent saphenofemoral valves):

A. With the tourniquet on the thigh the varices below the tourniquet fill slowly from below upward in from thirty-five to sixty seconds.

B: With the tourniquet removed the varices fill quickly from above downward (1 to 10 seconds).

These reactions occur when the valve function in the upper part of the great saphenous vein is deficient or absent permitting a reverse flow from the femoral into the great saphenous vein at the saphenofemoral junction in the fossa ovali.

Negative: (incompetent communicating valves):

A. With the tourniquet on the thigh the varices below the tourniquet fill rapidly.

B. When the tourniquet is removed the varices fill rapidly also.

This occurs when the valves of the communicating veins are incompetent resulting in a reverse flow from the deep to the superficial veins.

Double Positive (incompetent saphenofemoral and communicating valves):

A. With the tourniquet on the thigh the varices below the tourniquet fill quickly.

B. When the tourniquet is removed the veins immediately become more distended

This occurs when there is incompetency of the saphenofemoral valves and reverse flow takes place at the saphenous junction as well as through the incompetent perforating veins in the lower part of the limb.

Perthes Test (figure 386): This is carried out to determine if saphenous valve incompetency, communicating valve incompetency or deep vein obstruction is present (4).

TECHNIQUE: The patient stands and a tourniquet is applied

around the thigh to occlude the long saphenous vein but not the deep veins and he walks for five minutes.

Three types of reactions of the superficial veins may occur after walking. They may: 1) collapse; 2) appear unchanged, or 3) become more prominent and pain may occur.

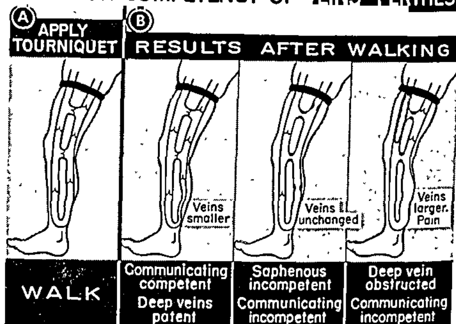


Figure 386 Perthes test The patient stands. A tourniquet is applied and he is instructed to walk (A). As a result (B) the veins may become smaller, they may remain unchanged in size or they may become larger and pain may appear.

INTERPRETATION: *Veins Collapse:* This occurs when the communicating veins are competent and the deep veins are patent. If, when the tourniquet is released, the veins fill in from thirty-five to sixty seconds the saphenofemoral valve is competent also.

Veins Unchanged. This indicates that the valves of the communicating and saphenous veins are incompetent. This interpretation is given because normally the valves of the saphenous and communicating veins are largely responsible for directing the

blood flow from the superficial system (low venous pressure area) to the deep system (high venous pressure area). With incompetent valves the pressure in the superficial veins would approximate that in the deep veins.

Veins Become More Prominent and Pain is Produced: This indicates that the deep veins are obstructed and the valves of the communicating veins may be incompetent.

Ochsner and Mahorner Test: (Modified Perthes test) (figure 387): The purpose of this test is to determine the location of incompetent communicating veins (5).

TECHNIQUE: A venous tourniquet is applied high on the thigh and the patient walks after which it is applied above the knee and he walks again. The tourniquet is then applied below the knee and he again walks. The veins below the tourniquet are observed immediately after each walking period.

Interpretation: If the varicosities below the tourniquet disappear on walking the communicating veins below the tourniquet are competent. If they are distended, incompetent communicating valves are present below the tourniquet.

Pratt Test: This is carried out to determine the location of incompetent communicating veins (6). Two tests are employed, #1 and #2.

Test #1: (figure 388): This test is to determine the location of incompetent communicating veins. The patient lies down. The leg is elevated and the veins massaged toward the heart to empty them. A tourniquet is placed high on the thigh to close the saphenous vein. An elastic (Ace) bandage is applied from the toes to the tourniquet. The patient stands and the bandage is unwound from top to bottom. The tourniquet prevents reflux of blood through the saphenofemoral valve and the Ace bandage compresses the veins below the tourniquet. The appearance of a bulge indicates the existence of an incompetent communicating vein. The area is marked on the skin with an indelible pencil.

Test #2: (figure 389) : This test is also to determine the location of incompetent communicating veins. The leg is elevated and the veins emptied. A tourniquet is applied at the thigh and an elastic (Ace) bandage is applied from toes to thigh. Another Ace bandage is applied over the tourniquet at the thigh.

The patient stands and the lower bandage is gradually unwound from the top to bottom and the upper bandage is wound on from the top down. If an incompetent vein appears between the bandages a bulge or blowout will occur. This point is marked with a skin pencil and the winding process continued. In this

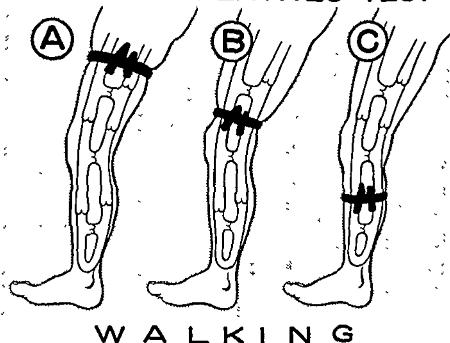


Figure 387. Oschner and Mahorner modified Perthes test. (A) A tourniquet is applied at the thigh and the patient walks. (B) The tourniquet is moved to above the knee and he walks again. (C) The tourniquet is moved to the calf and he again walks. Distended veins below the tourniquet mean incompetent communicator veins.

way multiple insufficient communicating veins can be detected.

Venous Pressure Tests: The pressure in the veins may be determined by: 1) observation of the amount of distention of the vein; 2) palpating the tension of the wall, or 3) direct measurement with an appropriate instrument (7). The purpose of the

test is to determine the presence or absence of deep vein obstruction. The tests are carried out at rest or after exercise.

At Rest: (figure 219): With the subject supine and the vein at the phlebostatic level (8) an elevated pressure often indicates venous obstruction of a large venous channel. Obstructions to small veins do not elevate venous pressure because of the rich venous collateral circulation.

Lewis Test: This is an indirect test for measuring venous blood pressure (9). The patient lies supine. One hand is placed on the iliac crest and the other on the bed. The prominence of the veins is noted; the positions of the hands are reversed and the distention of the veins noted again. Normally the veins of the elevated hand are collapsed while those of the hand on the bed are filled.

Exercise (figure 223): The effect of exercise on venous pressure has been discussed elsewhere.

DISEASES OF VEINS

The diseases of the veins which will be considered here are the following: 1) varicose veins with or without venous insufficiency; 2) thrombophlebitis; 3) thrombophlebitis migrans; 4) phlebothrombosis; 5) post phlebitic syndrome, 6) phlebosclerosis; 7) phlebofibrosis; 8) rupture; 9) phlebectasia, and 10) phlebospasm.

VARICOSE VEINS

These are dilated tortuous veins The valves in the veins may be competent or incompetent and thrombosis may or may not be present. Varicose veins are classified as primary and secondary.

Primary: These may be familial or non-familial. About 70 per cent of patients have a congenital weakness of the venous system in which the walls and valves of the veins are defective. Varicose veins are more common in females than in males because of the numerous large veins in the broad pelvis of the female. Primary varicosities may occur from weakening of the walls of the veins. The veins often are tortuous and venous insufficiency may or may not be present. The dilated veins may be objectionable cosmetically or produce pain. Swelling is not present and

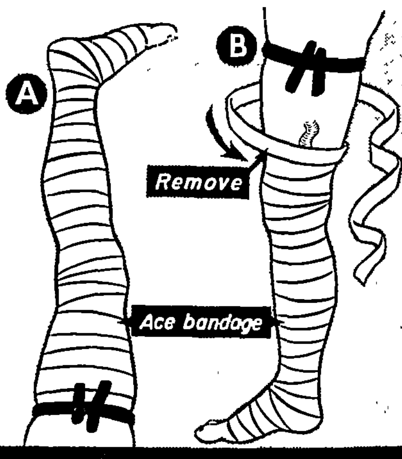


Figure 388. The Pratt #1 test: This is to determine the location of incompetent veins. The leg is elevated and is wrapped with an Ace bandage from the toes to the thigh and a tourniquet is applied around the thigh (A). The patient then stands (B) and the bandage is unwrapped slowly from the thigh to the foot until a varicose vein appears which is the site of an incompetent vein.

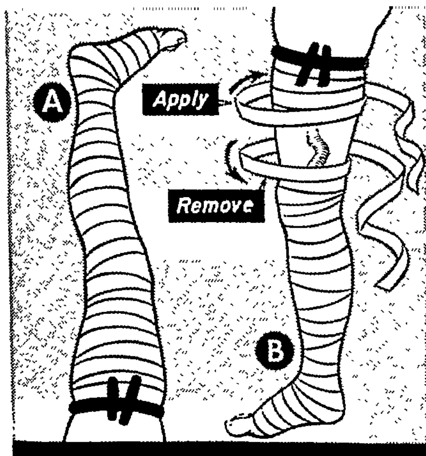


Figure 389. The Pratt #2 test: This is to determine the location of incompetent communicating veins. The leg is elevated and is wrapped from toes to thigh and a tourniquet applied (A). The patient stands (B) and the bandage is unwrapped from thigh to foot but at the same time another bandage is wound onto the thigh leaving a slit of skin visible between the two bandages. The appearance of a varicose vein indicates an incompetent communicating branch.

venous congestion is absent when venous insufficiency or thrombosis is absent.

Secondary: These may be associated with incompetent venous valves, thrombophlebitis, pregnancy, trauma, constricting bands, increased venous pressure from abdominal tumors or masses, heart disease, liver disease which produces portal hypertension or arteriovenous fistulas.

Pathologic Types of Varicosities: These are 1) simple varicose veins without insufficiency; 2) varicosities secondary to venous insufficiency; 3) post phlebitis, and 4) arterial varicosities (secondary to arteriovenous fistulas).

History and Physical Examination: Primary varicosities often are without symptoms but secondary varicosities have symptoms pertaining to the varicosities and to the underlying disease as well. Varicose veins without insufficiency or obstruction cause very few symptoms. The following symptoms are produced when some degree of insufficiency or obstruction is present. Aching pains in the calves is common when the long or short saphenous veins are involved. The ache is more intense on standing and is relieved by elevating the legs; however the pain may not disappear completely for a few hours. Often there is edema of the ankles which is at first pitting in type. Ocasionally there is itching, and scratch marks on the skin with secondary infection. As the disease progresses the skin becomes pigmented and ulceration above the internal malleolus occurs. The skin may be tight, shiny and hard. The varicosities may involve the genitalia. When AV fistulas are the cause of the varicose veins the history and physical examination often is as follows: Often dilated veins appear suddenly. The veins fill rapidly on dependency and remain partly dilated on elevation. The veins occur usually on the medial or posterior aspect of the leg or in the popliteal space. There is increased heat in the area of the communications due to the presence of arterial blood. A murmur and thrill often can be elicited. If a needle is introduced into the veins pulsations will be present. The oxygen saturation of blood in these veins is higher than in normal veins.

Special Clinical Tests: In order to prescribe accurately certain tests should be performed. These tests are for: 1) arterial circu-

lation; 2) deep vein patency; 3) saphenofemoral valve competency, and 4) competency of communicating valves.

Arterial Circulation: The arterial circulation is examined by questioning concerning intermittent claudication, performing the elevation and dependency test and palpating all available pulses. If the results of these tests are not decisive a plethysmographic study is conducted. If the arterial system is deficient surgical procedures must be considered carefully and vein injections usually are not employed because of difficulty of healing.

Deep Vein Patency. The deep veins may be tested by the following 1. The patient walks with the leg and thigh wrapped in an elastic bandage for sixty minutes, and if pain is produced the deep veins are probably not patent, 2. With the patient supine a thigh tourniquet is applied to occlude the superficial veins and the leg is elevated straight up and if the veins empty slowly deep vein obstruction may be present, 3. A venogram fails to show the deep veins when they are obstructed (figure 212).

Saphenofemoral Valve Competency. The Brodie-Trendelenburg test may be carried out (figure 385). A venogram with retrograde injection in the common femoral vein may demonstrate incompetency of this valve (figure 216). The patient stands and the common femoral vein is injected If the dye runs distally into the saphenous vein there is incompetence of these valves.

Competence of Communicating Valves· Incompetent communicating valves between the femoral and saphenous veins may produce varicosities These incompetent veins are revealed with the Brodie-Trendelenburg, Perthes, Ochsner and Mahorner and Pratt tests (figures 385, 386, 387, 388, 389).

Therapy: Certain general rules are followed (10): 1) *Varicose veins with competent saphenofemoral valves and competent communicating valves* Treatment may not be necessary unless the varicosity is painful or enlarging. Local injections are usually satisfactory.

2) *Incompetent saphenofemoral valve with competent communicating veins and deep valves.* Resection of the saphenous vein at the femoral junction is advisable. The saphenous vein should be stripped in its upper portion.

3) *Incompetent saphenofemoral valve and incompetent communicating branches:* The saphenous vein is resected, each incompetent communicating vein is resected and the long saphenous vein stripped between these points. The lesser saphenous is removed also.

4) *Incompetent saphenofemoral valve and incompetent communicating valve with ulceration of the skin:* The treatment is similar to 3 above but in addition compression bandages are applied to the ulcer and heat and elevation are employed to help heal the ulcer.

5) *Same conditions as 4 above but following phlebitis:* The same treatment is carried out as in 3 if the phlebitis is not active and if there has been at least *six* months after the acute phlebitic activity.

Contraindications to surgical treatment: These are active inflammation such as phlebitis, cellulitis or suppuration of an ulcer.

Arterial disease and venous insufficiency: Surgical treatment and injection treatment of veins may be carried out in patients with moderately advanced arterial disease providing small amounts of fluid are injected to prevent arterial spasm and providing vasodilating techniques are employed prior to the therapy for the veins.

Complications of Varicose Vein Surgery: These are the following: 1) injury to an artery; 2) hemorrhage; 3) infection; 4) post operative thrombosis. These are not common and do not offer special problems.

Varicose Vein Surgery During Pregnancy: Pregnancy is not a contraindication to active treatment of varicose veins. If the varicosities are mild elastic stockings and injections may suffice. In the presence of valvular incompetence ligation and stripping may be carried out.

THROMBOPHLEBITIS

This is an obstructive disease of veins which may be primary or secondary.

Etiology: Primary thrombophlebitis occurs without obvious cause. Secondary thrombophlebitis follows mechanical injury, muscular effort or strain, chemical injury from drugs, inflammatory

or suppurative diseases such as tuberculosis, syphilis, actinomycosis, ischemia, blood dyscrasias, for example polycythemia, leukemia or pernicious anemia.

History and Physical Examination: The symptoms and signs differ depending upon whether or not the process is acute or chronic and upon whether the veins involved are superficial or deep. The acute phase is associated with local pain, tenderness, fever, rapid sedimentation rate and leukocytosis while the chronic stage is associated with swelling, pigmentation and ulceration. Pain and tenderness over the tissues which overlie the vein, muscle cramps, local swelling and dependent cyanosis are common. Involvement of superficial veins produces local tenderness over veins which are often red and hot in the acute phase and are *cord-like and pigmented in the chronic phase. The signs and* symptoms will be discussed further under the individual veins involved.

Thrombophlebitis involving the following veins will be discussed: 1) Superficial veins of the body; 2) subclavian and axillary veins; 3) femoral and popliteal veins, 4) superior vena cava, and 5) inferior vena cava.

Superficial Vein Thrombosis: Thrombosis may occur in any of the superficial veins of the body. In the acute stage the vein is red, hot and swollen. In the subacute stage the temperature over the vein subsides and the lesion turns from red to brown. In the chronic stage only a cord may be felt under the skin. In some patients the brownish pigmentation of the skin remains permanently.

Subclavian or Axillary Vein Thrombosis (figures 373, 214): The subclavian vein passes anterior to the scalenus anticus muscle and posterior to the clavicle, and is subject to trauma by exercise which causes hypertrophy or swelling of the scalenus anticus muscle. Stretching of the axillary vein under the coracoid process or pectoralis minor may initiate thrombosis. Subclavian vein thrombosis occurs as a result of violent exercise or movement of the neck, thorax or shoulder girdle. A large first rib, a cervical rib, a fibrous band above the first rib or a calcified lymph node may exert pressure on the subclavian vein especially when the head and neck are in unusual positions. Persons who perform

work requiring extension of their arms above the shoulders are subject to thrombosis. Wrestlers, painters, weight lifters, ceiling cleaners and others who have hypertrophied neck muscles are *subject to this condition.* Carcinoma especially metastases from breast tumors may invade this vein.

History and Physical Examination: Usually the patient suffers acute pain in the shoulders and arm. This is followed by distention of the vein, edema and duskiness of the part. The cyanosis may be seen especially when the arm is dependent. After a few days collateral veins appear over the shoulder and chest. The edema often is massive and is pitting. It is reduced somewhat by elevating the part.

Prognosis: If due to trauma the prognosis is good as pulmonary embolus from this cause is relatively uncommon compared with emboli from the veins of the lower extremities. Usually within six months the edema subsides considerably due to recanalization of veins and to the development of collateral circulation.

Treatment: The part should be elevated and hot packs applied to overcome venospasm and the extremity should be put to rest until collateral circulation develops. Sympathetic nerve blocks may assist also in relieving venospasm. Anticoagulants are indicated. Anterior scalenotomy may be performed if the thrombosis is a result of a tight scalenus anticus muscle. If causalgia results sympathectomy is indicated, especially if sympathetic blocks are successful in relieving pain. In the presence of malignancy x-ray may be palliative.

Common, Superficial or Deep Femoral or Popliteal Vein Thrombosis: Obstructions to these veins obstruct the deep venous circulation from the leg.

History and Physical Examination: Thrombosis of the common femoral vein produces the "milk leg" which may occur after pregnancy. The entire limb becomes tense, swollen and painful. In the acute stages the femoral vein may be tender and hot. With superficial femoral vein obstruction swelling involves the upper thigh, knee, calf and foot. Deep femoral vein thrombosis produces tenderness and swelling of the thigh without swelling of the calf and foot. Popliteal vein thrombosis produces tenderness of the popliteal vein and swelling of the calf and foot.

Treatment: This varies with the size of the vessel involved and the cause of the thrombophlebitis. With secondary thrombophlebitis from polycythemia treatment directed to the underlying disease process as well as to the local defect is necessary. The aims of treatment are 1) to improve the local condition, that is to reduce swelling and heal ulcers, 2) to prevent emboli; 3) to prevent extension of the thrombus, and 4) to treat the underlying disease process. The following are helpful.

Elevation: The feet should be elevated four inches above the heart. This is accomplished best by elevating the foot of the bed using blocks.

Heat: Hot moist packs from foot to groin promote venodilatation and prevent venospasm. Heat has a dilating effect similar to that of a lumbar block. The technique of applying heat is as follows: Cold cream is placed on the skin to prevent maceration. One or two large towels are dipped in hot water, wrung out and wrapped around the extremity This is covered with a large loose rubber sheet and electric pads are placed on top of this. This remains in place for twenty out of twenty-four hours. After six days this treatment is discontinued.

Anticoagulants· Heparin and/or dicoumarol may be employed as anticoagulants (11). The former should be continued for about 1 week and the latter for about 8 weeks.

Nerve Blocks. Lumbar sympathetic nerve blocks may be employed if the patient has discontinued anticoagulant drugs. If anticoagulants are to be employed a catheter can be placed into the region of the lumbar sympathetics before anticoagulants are given. One per cent novocaine is injected periodically. Sympathetic blocks are used only when heat is not sufficient to reduce venospasm. Blocks often reduce pain considerably.

Avoidance of Dehydration· Fluid is forced orally or parenterally to prevent hemoconcentration. Low sodium fluids should be used to prevent edema.

Antifungus treatment: Desenex® powder and ointment are applied between the toes as needed.

Duration of Treatment: The patient is allowed out of bed when there is subsidence of local and general symptoms and after anticoagulants have been given in effective doses.

Treatment After Ambulation: Knee length elastic stockings for one or two years may be necessary to control edema (12). The foot of the bed should be elevated on 4 inch blocks and the legs should be elevated twice a day for half an hour. Swimming is advocated, heavy exercise is avoided and athlete's foot is treated. The patient is advised to resume anticoagulant therapy if the phlebitis returns.

Surgical Treatment: Iliac vein ligation may be performed to prevent emboli. In the presence of a femoral vein thrombosis the thrombus may be removed in some cases. It should be remembered that edema, varicosities and post phlebitic ulcers may occur after thrombosis or ligation of the common femoral vein.

SUPERIOR VENA CAVA THROMBOSIS: This is a severe disease which interferes with the return of blood from the head and the neck.

Etiology: Most obstructions are caused by carcinoma, aortic aneurysms, mediastinitis, syphilis and other diseases.

History and Physical Examination: The patient complains of swelling of the arms, chest and head. Edema, cyanosis of the head and dilated veins over the arms and trunk are apparent. Dizziness, syncope during exercise and prominent eyes with swelling of the conjunctiva are common.

Diagnosis: Elevated venous pressure in both brachial veins occurs (figure 222). Venograms made by injecting contrast material into both brachial veins usually show the obstruction clearly (figure 215A).

Treatment: Antiluetic treatment may help if the patient is syphilitic. A tumor if present may be removed in some cases or x-ray treatment may be helpful to reduce its size. Aneurysms in certain cases may be removed surgically or repaired. Resection of the superior vena cava and graft has been performed

INFERIOR VENA CAVA THROMBOSIS: This is an uncommon occlusive disease of the venous system.

Etiology: Thrombosis of the inferior vena cava occurs where there is a clotting tendency of the blood for example with blood dyscrasias or with neoplasm or by other causes.

History and Physical Examination: The symptoms consist of swelling and congestion of the legs. The signs are edema of both

feet, legs and thighs. There is distention of the veins of the dorsum of the feet and of the lower portion of the abdomen. The venous pressures in the lower extremities are increased as compared with those of the upper extremities (figure 222D). The blood flow in the superficial epigastric veins is from the groin toward the umbilicus instead of in the opposite direction which is usual (figure 215B).

Treatment: Anticoagulants should be given to prevent extention of the thrombus.

THROMBOPHLEBITIS MIGRANS

This is a recurrent type of thrombophlebitis which at times terminates fatally (13). The phlebitic process travels from one vein to another until marked interference with the venous circulation has occurred. The visceral veins may be involved as well as the veins of the limbs. Involvement of the hepatic vein produces hepatomegaly and portal hypertension. Involvement of the inferior vena cava and right heart may interfere with cardiac filling.

Etiology: The cause may be unknown; however a neoplasm such as carcinoma of the pancreas or lung often is present. Blood dyscrasias such as polycythemia, and the collagen diseases are etiologies.

Treatment: Heparin and dicoumarol are indicated in large doses. Often both of these agents are given together during the acute stage of the disease. Treatment of the underlying disease is essential.

PHLEBOTHROMBOSIS

This is an obstructive disease of veins characterized by an intravenous clot without an associated inflammatory reaction.

History: The disease was described by Ochsner and Debakey (14).

Etiology: The disease is thought to be due to venous stasis with alteration in the cellular and fluid constituents of the blood which results in the formation of a loose coagulum which is easily detached and results in pulmonary emboli. The disease is relatively common in elderly debilitated individuals who are forced to bed for long periods.

History and Physical Examination: The first *symptom often* is pain in the chest due to a pulmonary infarct. The disturbance in the chest may be mistaken for an upper respiratory tract infection or pleurisy. There may be pain on breathing, increased respiration rate and, in the more severe cases, chills and fever. Radiologically there may be signs of pulmonary infiltration. Examination of the legs shows tenderness of the calf muscle. Homan's sign is positive (sharp dorsiflexion of the foot produces pain in the calf). A palpable tender superficial venous cord in the calf is of diagnostic value. A slight increase in temperature in one calf as compared with the other is significant. Slight edema of one leg as compared with the other may be present. If the edema is below the knee the popliteal vein may be thrombosed. If the edema involves the thigh and leg the femoral vein may be thrombosed.

POST PHLEBITIC SYNDROME

This is an abnormal painful state of the limb which follows thrombophlebitis or phlebothrombosis (15, 16).

History and Physical Examination: After deep vein thrombosis especially of the larger veins there results swelling of the leg, pigmentation and induration of the skin especially around the ankles, chronic eczema and possibly ulcers usually superior to the internal malleolus. There is pain in the legs on standing or prolonged sitting with less pain on walking. Secondary varicose veins develop

Treatment: Elastic stockings and periodic elevation of the leg with avoidance of long standing is the treatment of choice. Pressure packs over the ulcer and correction of venous insufficiency when present may be helpful. Skin grafts may be necessary to facilitate healing of the ulcer.

PHLEBOSCLEROSIS

This is a calcified state of the veins (17). Chronic thrombophlebitis often is present. Pathologically the calcification usually occurs in the medial coat of the vein. The calcification may be diffuse or in the form of phleboliths. These are seen commonly

on x-ray examination of the pelvis and along the course of the veins of the legs (figure 207).

PHLEBOFIBROSIS

Fibrosis of veins occurs with hyperplasia of the fibrous tissues of the media. The veins usually are not dilated. The fibrosis is of unknown cause. There are no clinical symptoms and no effective treatment.

RUPTURE OF VEINS

This may occur after trauma or with increased intravenous pressure as during pregnancy or straining especially in patients with thin vessel walls and in those with incompetent valves.

PHLEBECTASIA

This is a dilatation of veins which occurs often as a result of increased intravenous pressure. This is usually associated with venous insufficiency but the veins are not necessarily varicose (tortuous).

PHLEBOSPASM

This is a pathologic amount of constriction which may occur as a result of severe pain or may be associated with thrombophlebitis or arterial embolus (18). The treatment is sympathetic blocking agents and local heat. Constriction of veins is common with stimulation of the sympathetic nervous system due to any cause, for example with fright or pain.

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Figure 390. Heinrich Ireaneous Quincke, 1842 to 1922. He was the first to describe angioneurotic edema and he introduced lumbar puncture as a diagnostic and therapeutic measure into medical practice. He first noted poikilocytosis and described pernicious anemia. He made significant observations on the capillary and venous pulse.

CHAPTER 47

Diseases of the Capillaries

EVIDENCE OF capillary damage should be searched for during the physical examination. The capillaries may show: 1) increased fragility, 2) increased permeability; 3) excessive vasodilatation; 4) excessive vasoconstriction; 5) an increased number; 6) a decreased number, or 7) thrombosis. Technics useful for studying these abnormalities are the Wright test, the Dalldorf test, the capillary filling test and scleral, retinal and nailbed microscopy.

INCREASED FRAGILITY: Petechiae of the skin often are a sign of increased capillary fragility. They often are more numerous on the lower limbs than on the upper limbs because the hydrostatic pressure is greater in the legs than in the arms when the patient is in the upright position. Abnormal fragility may be caused by vitamin C, K, or P deficiency; blood dyscrasias; for example thrombocytopenic purpura or leukemia; infections; for example streptococcus or meningococcus; malignant hypertension; arsenic poisoning or by other causes.

Tests for Capillary Fragility: These are the positive pressure tests such as the Wright test and the negative pressure tests such as the Dalldorf test.

WRIGHT TEST· This is a modification of the Rumpel Leede test (figure 391). Two circles 2.5 cm in diameter are drawn on the inner aspect of the forearm. The upper edge of the circles is 4 cm below the crease of the elbow. A sphygmomanometer cuff is placed above the elbow and is inflated to a mean arterial pressure (half-way between systolic and diastolic blood pressure). The cuff remains in place for fifteen minutes after which it is released. Five minutes after release, the number of petechiae within the circles are counted and the average count in the two circles is recorded Interpretation: Normal test, 10 spots or less. Borderline, 10 to 20 spots. Increased fragility, more than 20 spots (1).

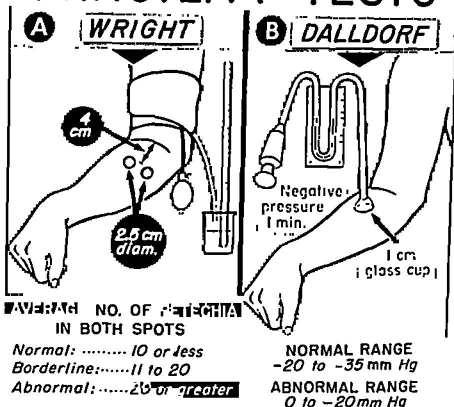


Figure 391. Wright modification of the Rumpel Leede test Two circles 2.5 centimeters in diameter are drawn on the inner aspect of the arm and a sphygmomanometer cuff is placed above the elbow and inflated to mean arterial pressure (A) (see text for explanation). Dalldorf test. A negative pressure is applied to the arm for sixty seconds after which the number of petechiae are counted (B) (see text for explanation).

Dalldorf Test (figure 391): A small glass cup with a diameter of 1 cm is applied to the skin. The cup is connected to a syringe so that a negative pressure can be produced. A manometer in the system shows the amount of suction (negative pressure) which is present. Suction is produced for 60 seconds after which the cup is removed. The smallest negative pressure which

produces petechiae is a measure of the resistance of the capillaries. Normally pressures of minus 20 to minus 35 mm of Hg do not produce petechiae. When petechiae occur at suctions less than minus 20 mm Hg capillary fragility is increased (2).

SCLERAL, RETINAL AND NAILBED MICROSCOPY: These have been discussed elsewhere (figures 262, 268, 271).

INCREASED PERMEABILITY: This usually manifests itself by swelling. The permeability of capillaries is increased when protein leaks through the capillary wall into the interstitial space (3). Common causes for increased permeability are angioneurotic edema, allergy, sensitivity to cold or heat, inflammation, anoxia or trauma (4). Tests for increased permeability are: 1) temperature tests for cold or heat allergy; 2) skin tests for pollen or dust allergies, and 3) trauma tests.

Temperature Test: Cold or heat allergy may be tested for by placing the part in cold or hot water and noting local swelling.

Skin Tests: Pollen, dust or food allergies may be detected by scratch or intradermal skin tests.

Trauma Test: An increased response to trauma is shown by rubbing a pencil across the skin which may produce swelling (dermographia) (5).

DILATED CAPILLARIES: In certain diseases dilated capillaries can be seen at the base of the nail with the naked eye, or capillary microscope. Giant capillary loops may be seen in Raynaud's disease, disseminated lupus erythematosus and scleroderma.

Nailbed Microscope (figure 271): This instrument makes it possible to examine the structure of the capillaries and observe the hemodynamics. This is of particular value during attacks of Raynaud's phenomenon (figure 275).

Ophthalmoscope (figure 267): Capillary aneurysms can be seen in the retina with this instrument and appear as small red dots.

Scleral Microscope (figure 268): Aneurysms may be seen also in the scleral vessels with this instrument with a 50 to 120 times magnification

CONSTRICTED CAPILLARIES: Pale tissues may be due to constriction of the capillaries. Constriction of individual capillaries cannot be seen with the naked eye; however, they can be seen with the nailbed or scleral microscope. During the white stage of the

Raynaud's phenomenon the capillaries of the nailbed are either constricted or empty or both (figure 275A).

INCREASED NUMBER OF CAPILLARIES: When the number of capillaries is increased at the base of the nail, the skin appears pink or red. This is typical of local inflammation. Individual capillaries cannot be seen with the naked eye but they may be seen with the capillary microscope.

DECREASED NUMBER OF CAPILLARIES: This occurs often with scleroderma and appears as pale skin at the base of the nail. The decrease may be due to organic or functional changes. With scleroderma the capillaries are destroyed and are replaced by collagen and other tissue. With Raynaud's disease the decrease in number of capillaries often is functional and temporary.

THROMBOSED CAPILLARIES: These are seen typically in advanced Raynaud's disease and with thromboangiitis obliterans and can be seen at the base of the nail with the naked eye, with a hand lens or with a nailbed capillary microscope.

Capillary Filling Time Test: The purpose of the test is to demonstrate abnormalities of capillary filling which may be due to organic or functional disease of capillaries or arteries which prevents capillary filling.

TECHNIC: The hand is clenched rapidly and repeatedly for 30 seconds and is then opened part way. In the absence of disease a normal skin color returns to all areas in a few seconds. With disease, certain areas of skin fill slowly (often as long as 30 seconds). The hand should not be opened to full extension as this stretches the skin tightly and limits capillary filling. To determine if the delayed filling is due to functional or organic disease, the test is carried out before and after blocking sympathetic nerves.

Other Tests: Additional tests used for studying diseases of the capillaries are related to purpura and are discussed under the heading of Increased Capillary Fragility (Purpura).

INCREASED FRAGILITY

THROMBOCYTOPENIC PURPURA

Thrombocytopenic purpura which is characterized by a low platelet count may be primary or secondary.

Primary Thrombocytopenic Purpura

Purpura Hemorrhagica or Werlhoff's Disease

This is a disease of unknown cause which is characterized by ecchymosis and petechiae formation involving ectodermal surfaces, and is associated with a decrease in blood platelets.

Age, Sex and Race: The disease is common in young women but may appear before puberty or after fifty. It is approximately twice as common in females as in males. It is more common in the White than in the Negro race.

Etiology: This is unknown. The disease has been reported in more than one member of a family but has no consistent generic pattern (6).

History and Physical Examination: The complaint is usually that of easy bruising of the skin, nosebleeds, bleeding from the gums, blood in the conjunctiva, urine or stool or profuse menstrual bleeding. The spleen is slightly enlarged in 10 or 15 per cent of patients but rarely is huge Hemiplegia may be present if there has been bleeding into the central nervous system. Chronic leg ulcers may be present (7, 8).

Laboratory Findings. During acute attacks the platelet count is low, often in the neighborhood of 30,000 which is usually associated with bleeding. The platelets themselves may be abnormally large and granule-poor. The bleeding time is prolonged, often for hours, which is a manifestation of defects of the blood and blood vessels. The clot retraction time is prolonged but the coagulation time is normal The Wright Test (tourniquet test) is positive which gives evidence of the weakened capillary bed and decreased number of platelets. A secondary anemia may be present (9). The leukocyte count is usually normal; however, it may be increased if there is a large hemorrhage into the tissues. The number of megakaryocytes in the bone marrow may be normal or increased and atypical granulation in the cytoplasm of these cells may be present.

Clinical Types: The disease may be acute or chronic. Acute thrombocytopenic purpura affects young individuals, has a sudden onset and may be associated with infectious processes or may occur without obvious cause. A spontaneous remission in the

blood platelets may occur in four or five months. Eosinophilia and lymphocytosis may be present. Chronic purpura affects older persons and may be persistent or characterized by remissions and exacerbations.

Differential Diagnosis: The disease should be differentiated from: 1) secondary thrombocytopenic purpura; 2) leukemia; 3) hypersplenism, and 4) aplastic anemia. Secondary purpura is suggested by the presence of a sore throat, arthralgia, and leukopenia or neutropenia preceding the appearance of the purpuric spots. Leukemia is suggested by immature leukocytes in the blood smear and hypersplenism or aplastic anemia are suggested by neutropenia and by typical bone marrow pictures.

Treatment: The acute and chronic forms are treated as follows: 1) Transfusions of fresh blood are given. Polycythemic blood transfused through siliconed apparatus to preserve the platelets is effective (10). Fresh transfusions just before splenectomy may prevent bleeding during surgery. 2) Prednisone, cortisone, and ACTH are often of value. Large doses of these agents may be required (600 mg of cortisone for 5 to 10 days). Ultimately, small doses such as 5 mg of prednisone daily may be sufficient to maintain a remission. A low sodium, high protein, high potassium diet is employed to prevent water retention if cortisone is given. 3) Splenectomy is performed when conservative measures fail, providing the surgical risk is not great. Splenectomy is successful in about 75 per cent of patients.

Secondary Thrombocytopenic Purpura

These are the thrombocytopenic purpuras with a known cause.

Etiology: Thrombocytopenia results from the various factors listed in the classification. The etiologies include various vascular defects, blood dyscrasias, infections, malignancies, drugs, chemical agents and physical factors.

History and Physical Examination: The history is that of the underlying abnormality and the presence of purpuric spots, petechiae, or hemorrhage.

Laboratory Findings: The blood platelets are low, with depression of the megakaryocytes of the bone marrow. Total aplasia of the bone marrow may be present when aplastic ane-

mia is the basic disease. Positive local skin reactions to patch tests of the offending agent may be present if allergies are the cause.

Treatment: 1) BAL is almost specific for heavy metal poisoning such as occurs with gold. 2) Fresh whole blood transfusions to supply platelets and red cells are indicated. 3) Prednisone or cortisone may increase capillary resistance. 4) Splenectomy has been performed in certain cases but generally it is less successful than with primary thrombocytopenic purpura.

Thrombotic Thrombocytopenic Purpura

Thrombocytic Acro-angiothrombosis, Thrombocytopenic Verrucal Angionecrosis

This is a purpura which is, in part at least, secondary to a vascular defect, and is a rare, usually fatal disease characterized by purpura, hemorrhage and fever associated with platelet thrombosis of vessels and thrombocytopenia.

History: This disease was first described by Moschowitz in 1925 (9, 11).

Age and Sex: There is no particular age or sex distribution.

Etiology: This may be a collagen disease in which the endothelium and subendothelium of the vessels are affected, which favors platelet thrombi. The thrombocytopenia may result from removal of platelets from the blood stream by precipitation of platelets in the vessels, however certain cases have been reported in which a defect in platelet formation was present.

Pathology (figure 392): The heart, lungs, kidney, liver and spleen are involved. There is wide spread occlusion of small arteries, arterioles, capillaries and venules by granular, hyaline-like masses. The masses project from the side of the vessel and encroach on the lumen. Fibrinoid degeneration of the subendothelial tissue is present. The hyaline-like masses often are associated with platelet deposits and fibrin with occlusion of the vessel. Inflammatory reactions in the walls of the adventitia usually are absent.

History and Physical Examination: The history is that of weakness, fever, black and blue spots on the skin, gross hemorrhage, general nervousness with or without neurologic signs.

There may be shortness of breath or abdominal pain and purpuric lesions may be present in the skin. Abnormal neurologic findings may be present such as a positive Babinski test or altered reflexes. Abdominal tenderness may indicate visceral involvement. The cranial nerves may be abnormal. Transient hemiplegia or mono-

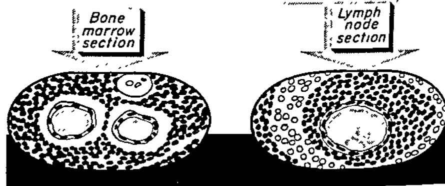


Figure 392. Pathologic findings in patients with thrombotic thrombocytopenic purpura

plegia may be present. Rales in the chest suggest myocardial failure or patchy consolidation of the lungs. Clinical findings of pneumonia are not uncommon. Enlargement of the liver and spleen may be observed.

Laboratory Findings: Anemia of the hemolytic type may be

present. Evidence of erythrocytosis (normoblasts and reticulocytes) often is present. Biopsy of the skin may show characteristic pathologic findings. Leukocytosis is common. Thrombocytopenia with a platelet count of less than 40,000 is common. Bone marrow examination shows a normal number of megakaryocytes but little evidence of formation of platelets. The bleeding time is prolonged greatly and the clotting and prothrombin times may be moderately prolonged The icterus index may be elevated slightly due to a hemolytic anemia. Blood tests for clot retraction, coagulation and bleeding time, platelets, cold globulins and gelling of protein of serum should be performed (vide infra).

Clot Retraction Time: Two ml of blood are placed in a round-bottomed test tube, 15 mm in diameter which is put into the incubator at 37 degrees C Beginning retraction occurs in one to two hours and is complete in eighteen to twenty-four hours.

Coagulation Time: One ml of blood is taken in a 1 ml syringe previously rinsed with isotonic sodium chloride and is placed in a test tube measuring 8 mm in its internal diameter which has been previously rinsed with isotonic sodium chloride. The tube is tilted every thirty seconds until the blood becomes solid Normally the time from withdrawal of the blood to coagulation is from five to ten minutes The test is carried out at a room temperature of 65 to 90 degrees F (12).

Bleeding Time: The ear is punctured deeply with a #11 Bard-Parker blade and the blood is blotted with a piece of filter paper every 30 seconds until the flow ceases. The drops decrease in size as the bleeding slows down. The first blot should be 1 or 2 cm in diameter. The normal time measured to the cessation of bleeding is one to three minutes (12).

Platelet Count: For this test a red cell counting pipette is used with the diluting solution made as follows: One hundred ml of 3 8 per cent sodium citrate solution, 0.2 ml of 40 per cent formaldehyde solution and 0.1 Gm of brilliant cresyl blue are mixed together and used fresh. The diluting fluid is drawn up near the 1 mark on the pipette. The ear lobe is stabbed and blood is drawn to the 0 5 mark and then diluted to the 1.01 mark. This makes a final dilution of 1:200. The pipette is handshaken for 2 minutes

and the counting chamber is filled. Ten minutes are allowed for the platelets to settle. The counting is the same as for an ordinary red cell count. Platelets and red cells may be counted in the same fluid. Normally there are 250,000 to 300,000 platelets per cu mm of blood (13).

Cold Globulins (Cryoglobulins): Blood is drawn and allowed to clot at room temperature in a clean test tube. After the clot has formed, the serum is observed and is found to be fluid and clear. The tube then is placed on the bottom shelf of the refrigerator at 4 degrees C for six to twenty-four hours and observed periodically for a white flocculate which represents a precipitation of globulins. This disappears when the tube is brought to room temperature (14).

Prothrombin Test: A variety of techniques may be employed. The one described below is that employing Simplastin.*

General Remarks: The glassware should be kept scrupulously clean with soft soap and rinsed thoroughly after each use. Synthetic detergents should not be employed. Preferably glassware should be restricted to the prothrombin test and not used for other purposes. Distilled water of good quality should be used. The room temperature should not exceed 75 degrees F. Blood plasma is employed. Blood is withdrawn by a clean venapuncture. Immediately 4.5 ml of blood is added to 0.5 ml of a molar solution of sodium oxalate (13.4 grams anhydrous sodium oxalate, reagent grade, in distilled water to a total of 1000 ml). The tube is immediately tilted to obtain good mixing. The oxalated blood is centrifuged at 1700 revolutions per minute for ten minutes. The clear plasma is drawn into a test tube and stored in the refrigerator. The prothrombin time should be determined as soon as possible, preferably within four hours.

The Test: To the "6 determination vial" of Simplastin, 1.6 ml of distilled water is added. The Simplastin already contains calcium and sodium chloride in proper amounts. The solution is shaken briefly. The plasma to be tested is placed in a water bath of 37 degrees C for five to ten minutes. Two-tenths ml of Simplastin suspension is pipetted into a test tube and placed in a

* Warner-Chilcott Company.

water bath of 37 degrees C for three minutes. With a 0.1 ml micropipette 0.1 ml of whole or diluted plasma also adjusted to 37 degrees C is transferred to the tube containing 0.2 ml of Simplastin suspension. The pipette is blown out quickly and the stop watch started simultaneously. The bottom of the tube is tapped sharply to mix the contents A #22 nichrome wire loop stirrer is inserted immediately into the tube. The loop is moved across the bottom of the tube in sweeping motions about two times a second. When the clot appears, the watch is stopped and the time recorded.

INTERPRETATION: The concentration of prothrombin in the plasma is read from the curve or when anticoagulants are being administered, the time should be twice the control time This is *considered an effective but safe anticoagulant level.*

Tests for Gelling: The blood is allowed to clot in a clean, dry test tube, and the serum is observed at room temperature. Normally the serum should be liquid, however gelling may occur in such diseases as multiple myeloma.

Differential Diagnosis: Thrombotic thrombocytopenic purpura is differentiated from systemic lupus erythematosus by the thrombocytopenia, the widespread occlusion of the small vessels and the absence of the L E. phenomenon The frequent association of spenic involvement with thrombotic thrombocytopenic purpura suggests hypersplenism which may be associated with this disease but probably is not a primary phenomenon.

Prognosis: Termination has been fatal in the majority of cases cited.

Treatment: Cortisone and ACTH may be of value; however the effect may be transient. Splenectomy has been suggested in early cases. Supportive measures and fresh blood transfusions may be of value.

NON-THROMBOCYTOPENIC PURPURA

Non-thrombocytopenic purpuras may be primary or secondary. The primary forms include: 1) senile purpura; 2) purpura simplex, and 3) hereditary hemorrhagic diathesis (see classification above).

Primary Forms

Senile Purpura

This is a benign disease of elderly persons characterized by purpura of the skin.

History and Physical Examination: The patient complains of purpuric spots on the skin which occur either spontaneously or as the result of mild trauma. The lesions may last for three or four weeks and then fade. Examination shows ecchymotic areas with well defined borders. The lesions are on the extensor surfaces and radial aspect of the forearm and back of the hands and do not involve the fingers. The skin is thin and the vessels are tortuous and dilated.

Laboratory Work: The capillary fragility test (Wright Test) is normal. The hemorrhage is thought to result from inadequately protected and supported vessels rather than from weak vessels.

Treatment: Vitamins K, C and rutin are of little value. Protection from trauma and symptomatic treatment are indicated. Prednisone, prednisolone, cortisone and ACTH usually are not effective.

Purpura Simplex

This is a mild form of purpura without associated systemic disease or exciting agents. It is seen primarily in women. Capillary fragility tests and tests for blood coagulation are normal. Because of the benign nature of this disease no treatment is indicated.

Hereditary Hemorrhagic Diathesis

Hereditary Hemorrhagic Thrombasthenia, Athrombotic Purpura, Pseudo-Hemophilia, and Constitutional Thrombopathy

This is an hereditary bleeding tendency characterized by a prolonged bleeding time, normal platelet count and a variable, though usually normal, coagulation time and clot retraction time.

Etiology: This is an inherited vascular disturbance (15).

History and Physical Examination: Nosebleeds, black and blue spots, profuse menstrual bleeding or bleeding from the gums as a result of slight trauma are present.

Laboratory Findings: The bleeding time may be either prolonged or at the upper limits of normal. The platelet count, retraction time and the capillary fragility tests are normal. Abnormal capillary loops may be present in the nail bed (15).

Differential Diagnosis: The disease should be differentiated from hemophilia, idiopathic thrombocytopenic purpura and vascular purpura. Hemophilia has a coagulation time which is increased and a bleeding time which is normal. Idiopathic thrombocytopenic purpura has a low platelet count. Vascular purpura is characterized by a normal bleeding time and a positive tourniquet test.

Treatment: Protection against trauma is important. If trauma should occur pressure bandages should be applied. Blood transfusions and splenectomy are not of consistent value.

Secondary Forms

These include stasis purpura, traumatic or mechanical purpura, allergic or anaphylactoid purpura including Schonlein-Henoch purpura and purpura fulminans, and those purpuras which appear secondary to skin diseases, chemical agents, systemic diseases, infections, avitaminosis and hyperglobulinemia

Stasis Purpura

This may result from stasis of blood in the lower extremities and is associated often with venous insufficiency.

Traumatic or Mechanical Purpura

This may result from constriction of tissues of any sort, for example, from tight garters.

Allergic or Anaphylactoid Purpura

Schoenlein and Henoch Purpuras

This is a systemic allergic response to infections or allergens. This syndrome is characterized by purpura associated with gastrointestinal manifestations, painful swelling of the joints, albuminuria and hematuria.

Age and Sex: The disease primarily affects children from three to fourteen years of age, although it has been reported in elderly patients. Both males and females are affected.

Etiology: The disease is thought to be an allergic response characterized by increased permeability of the capillaries with loss of plasma and red cells into the tissues. Hematopoiesis is normal.

Pathology: There is an acute exudative inflammatory reaction around the small vessels and capillaries of the superficial layers of the corium with edema of the epidermis. Necrotizing arteriolitis and tissue eosinophilia may occur. Focal lesions affecting the jejunum, ilium, central nervous system and kidney may be present.

History and Physical Examination: The onset is often with fever, abdominal cramps, gastrointestinal hemorrhages, swollen joints and purpura of the skin. The purpura may be symmetrical and located on the extremities Purpura alone may be present or wheals with minimal purpura may occur. Erythema nodosum or necrosis of the infiltrated areas may be present. Attacks of abdominal pain are common at night. Epileptiform attacks suggest involvement of the central nervous system.

Laboratory Findings: Albumin and blood are present in the urine. The blood count may be normal or elevated. Eosinophilia may be present. The stools may contain blood. The capillary fragility test (Wright Test) is normal.

Treatment: 1) Ephedrine sulfate, $^3/_8$ grain, three times a day has been employed. 2) Epinephrine, 0.3 ml of 1:1000 solution is employed in acute cases. 3) Antihistamines such as tripelannamine hydrochloride (Pyribenzamine) 150 mg daily may be helpful. 4) Prednisone, prednisolone, cortisone and ACTH may be employed. Snake venom, vitamin C, vitamin P, rutin, foreign protein, and salicylates have not been of significant value.

Purpura Fulminans

This is an acute, progressive, usually fatal non-thrombocytopenic purpura often associated with severe infections

Etiology: This may be an allergic response to infection and may be associated with hemorrhage into the adrenal cortices (The Waterhouse-Friderichsen's syndrome).

Treatment: Huge doses of cortisone intravenously (Solu Cortef®) with a low sodium, high potassium diet are indicated. Exchange transfusions may be tried Rapid control of the infection should be brought about with antibiotics which are selected on the basis of the organism which is present. If the organism is not known, a wide spectrum antibiotic (penicillin plus streptomycin) should be used.

History and Physical Examination: A history of scarlet fever or other infection followed by a latent period and then the development of an acute purpura is common. The blood pressure often is low and the patient is in shock.

Skin Diseases, Chemical Agents, Systemic Diseases, Infections and Avitaminosis

Purpuric spots or petechiae may occur as a result of diseases of the skin, generalized systemic diseases, infections, avitaminosis and following ingestion of chemical agents

Etiology: Iodides, belladonna, atropine, bismuth, mercury, acetophenetidin, acetylsalicylic acid, chloral hydrate, merbaphen, penicillin and quinine have produced purpura. Subacute bacterial endocarditis, meningococcemia, Rocky Mountain spotted fever, typhus fever, scarlet fever, small pox, malaria, measles, diphtheria, influenza, tuberculosis and systemic lupus erythematosus are causes. Liver disease produces purpura associated with prothrombin or fibrin deficiency or from increased capillary fragility. Nephritis, rheumatic fever and hemochromatosis have been implicated. Scurvy (deficiency of vitamin C) and deficiency of vitamin P may result in capillary weakness (16).

History and Physical Examination: The history is that of ingestion of an offending drug or the presence of an underlying disease. Examination reveals the purpuric manifestations of the disease and the characteristics of the disease itself.

Laboratory Findings: Often laboratory tests are not abnormal, however abnormal liver function tests or kidney function tests are found. Blood cultures may be positive in certain cases.

Treatment: This consists of: 1) removal of the underlying cause; 2) treating shock when present; 3) administering prednisone or cortisone; 4) giving exchange transfusions; 5) forcing

fluids, and 6) prescribing high vitamin dosage, especially vitamin C.

CRYOGLOBULINEMIA

This is a non-thrombocytopenic purpura associated with increased sensitivity of the serum globulins to cold.

Etiology: The usual cause is multiple myeloma.

History: Purpura is the usual presenting complaint. Nasal hemorrhage and bleeding from the gums are common. There may be a history of sensitivity to cold and the patient may have the Raynaud's phenomenon if cold globulins are present.

INCREASED CAPILLARY PERMEABILITY

Increased capillary permeability is associated with swelling of the part usually due to leakage of blood vessels. Angioneurotic edema, serum sickness, allergy, physical irritants and inflammations will be discussed.

ANGIONEUROTIC EDEMA

This is a type of giant urticaria which usually involves the face and may be recurrent in nature (17).

Age, Sex, Race: The disease usually appears first at puberty. Both sexes and all races are involved.

Etiology: Allergy to foods, drugs and infections, as well as hormonal factors have been causes. The disease usually is idiopathic; however in certain cases the disease appears to be hereditary.

Pathology: The interstitial spaces are filled with edema fluid which is high in protein content as compared with the lower protein content that is present in the edema fluid of patients with cardiac failure and nephritis. Leukocytes are often present.

History and Physical Examination: There is a sudden appearance of swelling often involving the eyes, cheeks, lips, mouth and glottis. Swelling of the glottis may interfere with breathing. The swelling once it occurs may last for from one to three days and often fails to respond to epinephrine.

Laboratory Work: Passive transfer tests are negative and skin tests usually are not informative.

Prognosis: Death may occur from strangulation. The prognosis is better in the non hereditary cases.

Treatment: The cause if known should be removed. Large doses of prednisone, ACTH and antihistamines should be employed. Epinephrine, ephedrine and cold applications may be helpful. Tracheotomy may be necessary.

SERUM SICKNESS

This is an allergic reaction resulting from the parenteral administration of a foreign serum characterized by an incubation period, skin eruptions, enlargement of lymph nodes, fever, edema and polyarthritis.

Age, Sex and Race: All ages and both sexes are affected.

Etiology: Foreign protein such as egg white or horse serum.

History and Physical Examination: From six to twelve days after the injection of foreign protein there appear arthralgia, fever and edema The face, sacral, pretibial regions, ankles, hands and arms are the areas where it is most often noted. Oliguria, albuminuria, nitrogen retention and other signs of renal insufficiency may appear.

Treatment: This is the same as for angioneurotic edema.

URTICARIA

Urticaria is often produced by infections from bacteria, protozoa, worms, arthropods, insect bites, foods or drugs, inhaled pollens, dust, external contact and physical agents, such as cold, heat, ultraviolet irradiation, etc. Liberation of acetylcholine from emotional disturbances may be the cause in some cases.

Age, Sex and Race: All ages, sexes and races are affected.

History and Physical Examination: There is acute or slow development of sharply defined urticarial wheals which may be localized or disseminated and may vary in size from several millimeters up to several inches in diameter. Often itching, nausea vomiting and diarrhea are present also. Often old urticarial wheals disappear as new ones develop.

Treatment: The offending foods, pollens, drugs, inhalants, or parasites are eliminated and emotional disturbances should be controlled. Bacterial infections should be treated.

PHYSICAL IRRITANTS

Increased capillary permeability may be produced by trauma, cold, such as frost bite, trench foot, immersion foot or pernio, heat and excessive exposure to ultraviolet light (18, 19, 20, 21).

INFLAMMATION

Inflammatory lesions may be bacterial or non-bacterial. Either of these is associated with increased capillary permeability, often being present as urticarial lesions. Treatment is by removing the cause and by giving appropriate therapy as outlined under angioneurotic edema.

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CHAPTER 48

Diseases of the Lymphatic System

THIS CHAPTER contains a discussion of lymphedema and lymphangitis. Tumors of the lymphatic system are discussed in the chapter on tumors of the vascular system (chapter 49).

General History Relative to Diseases of the Lymphatic System: The history should contain information relative to the presence of edema at birth. Milroy's disease and congenital lymphedema with or without amniotic bands are present at birth. A family history of edema also is important. Milroy's disease is characteristically hereditary and congenital and a history of edema at birth will be found in certain members of the family. The age of onset of the edema should be recorded. Lymphedema praecox has its onset characteristically at the time of puberty. The history may help to determine if the lymphedema is of the primary or secondary type. A history of surgery in which the lymph glands have been removed would suggest that the edema was secondary. A past history of enlarged lymph glands may represent neoplastic invasion of these structures which would explain the nature of the lymphedema. A past history of lymphadenitis or of lymphangitis following infections of any sort is important. Trauma from burns or lacerations should be recorded. Previous x-ray treatment may be a cause of lymphedema. Previous residence in a tropical country with exposure to filariasis should be noted. Disease states such as tuberculosis and syphilis should be considered A past history of phlebitis or prolonged dependency of the legs is of importance. A history of the effect of dependency and elevation on the edema is an aid in determining the origin of the edema. Characteristically elevation of the limb for twenty-four hours does not improve lymphedema while the edema of venous obstruction or congestive failure subsides considerably after this period of elevation

General Physical Examination Relative to Diseases of the Lymphatic System: This examination should be carried out so that all portions of the extremities are easily seen. If the edema is due to erysipelas, the leg will be red and inflamed and if due to neoplastic invasion of lymph nodes the lymph glands may be enlarged. Palpation of the edematous areas is of importance. Lymphedema is characteristically hard and non-pitting. When the edema is acute and due to inflammation of lymphatic vessels the protein content of the interstitial fluid is high and the tissue pressure is often greater than that encountered in edema of other origins. With chronic lymphedema the protein elements of the subcutaneous tissue are replaced by fibrous tissue which sometimes is referred to as fibroedema which is hard and non-pitting. Examination of the veins is of particular importance to rule out venous insufficiency or venous obstruction as a cause for the edema. Careful observation should be made to determine if the edema is local or generalized. Generalized edema is common in nephritis, nutritional deficiency and congestive heart failure whereas lymphedema usually is local.

LYMPHEDEMA (PRIMARY)

MILROY'S DISEASE

This is a congenital and hereditary lymphedema (figure 393).

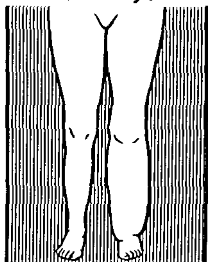
History: The disease was first described by Milroy in 1892 (1) and was redescribed in 1928 (2). Milroy pointed out that this disease was both congenital and hereditary and the diagnosis should be reserved for these cases (3).

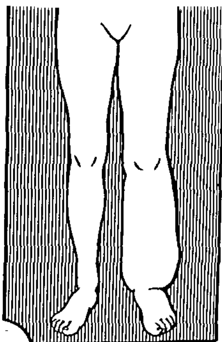
Sex and Age: Males and females are affected alike. The disease is present at birth.

Etiology: Some workers have suggested that incompetence of the valves of the lymphatic system is responsible in some cases. In certain cases there may be a local congenital abnormality of the lymphatics which results in swollen white spots which actually are lymphatic lakes There may be a diffuse failure of development of the lymphatic system or an abnormal development of the lymphatics with lymphangiectasia.

History and Physical Examination: The edema is present at

LYMPHEDEMA
(PRIMARY)





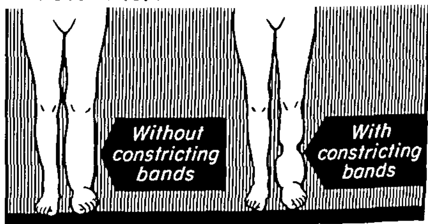


Figure 393. Primary types of lymphedema.

birth. It may involve one or two limbs. It may gradually progress or it may show no progression. The edema is usually painless and the health is otherwise good. The edema is of the pitting type and usually involves the feet and extends up the legs to the knees. Often there is a rosy hue of the swollen area and this color fades on pressure but rapidly returns when pressure is released. Scattered on this rosy background are white spots, often 1 cm in diameter which are not present on the normal portions of the limbs. Ulceration is absent. The edema is not altered by elevation or dependency.

Pathologic Anatomy: Biopsy shows large lymph spaces and fibrous tissue which has replaced the subcutaneous tissue (4). There is no evidence of inflammatory disease. Often there is obliteration of the papillae of the skin and absence of sweat glands. Blood vessels may be compressed by the edematous areas. Fragmentation of collagen occurs from the traumatic effects of the edema. Vascular infiltration of the dermis may occur. Abnormalities of the lymphatic walls may develop. Occasionally fat sloughs occur and muscles, tendons and bones atrophy.

Diagnosis: The criteria for diagnosis as laid down by Milroy are: 1) a congenital and hereditary condition with a steady growth corresponding to the normal growth of the body until adult size is reached; 2) limitation of the edema to one or both lower etxremities, the areas involved being variable but most often confined to below the knees; 3) permanence of the edema, and 4) absence of local pain.

Treatment: Elastic stockings, intensive antibiotic treatment if cellulitis should become superimposed on the edematous legs, and encouragement are the treatments of choice. Light massage and compression is of slight help When the disease is advanced and the limb unwieldy, especially when it interferes with mobility, surgical treatment is indicated. In these cases the voluminous skin and subcutaneous tissue can be excised and the lymph vessels which run through the muscles are utilized for drainage. Enzyme therapy, that is an enzyme to hydrolyze the hyaluronic acid, a viscous polysaccharide which is found in the interstitial spaces, has been suggested but is not always successful. Sutures have been employed to produce new channels under the skin. This

has not been successful uniformly. Sympathectomy generally has not been helpful. Ligation of lymph channels in order to divert the lymph into more normal channels is difficult because of the problem of locating the incompetent lymphatic vessels. Lymphangiectomy in which the edematous tissue is removed and the muscle and fascia covered by skin grafts from the original excised skin has been employed with some success when the limb is gigantic.

CONGENITAL LYMPHEDEMA

Without Constricting Bands

Edema of the leg is present at birth and is characterized by a diffuse swelling of the foot, leg and sometimes the thigh. The abnormality is not hereditary (5). Inflammatory and neoplastic conditions which interfere with lymphatic drainage are absent (figure 393).

Pathology: The skin and underlying cellular tissue are thickened. The subcutaneous spaces are filled with dilated lymphatic spaces and are surrounded by fibrous tissue and are true diffuse lymphangiomas.

Treatment: This is usually conservative with elastic stockings; however excision of the excess tissue has been carried out in some cases.

With Constricting Bands

Edema is present below an annular zone of sclerosis thought to be due to an amniotic band which was present prior to birth (5). Above the constriction the leg is normal. Below it is swollen, hard and may be cyanotic (figure 393).

Treatment: Excision of the sclerosed zone.

LYMPHEDEMA PRAECOX

This is a tense pitting edema of slow onset which is found in young women (6, 7) (figure 393).

Etiology: Unknown.

Sex and Age: This affects young girls, especially at puberty (12 to 15 years). It is uncommon in men. The external genitals may be involved.

History and Physical Examination: Gradual development of painless edema often on the side of the foot may be present. The edema is present especially in the evening on retiring. It is increased with activity or during the menstrual period or in hot weather. It disappears temporarily during rest. In the early stages there is no edema on arising in the morning. After a few years the edema progresses to the top of the leg becoming increasingly marked and it is less reducible by recumbency. It is often confined to one leg but frequently a similar disturbance occurs in the opposite leg. Large ulcerations are rare but small skin ulcers with lymphorrhea may occur. Acute lymphangitis is common.

Treatment: Conservative measures such as elevation, elastic stockings and light massage without trauma may be of advantage. Antibiotics should be used for lymphangitis. Lumbar sympathectomy has been tried but without uniform success. Femoral vein ligation has been carried out as it was noted that the femoral vein was at times large. Success has not been consistent with this procedure. In advanced cases extensive surgery may be performed in which the voluminous skin, subcutaneous and lymph tissues are excised and drainage of lymph is carried out by way of the lymph channels in the muscles. Skin grafts are used.

LYMPHEDEMA (SECONDARY)

POST LYMPHANGITIC LYMPHEDEMA

This is lymphedema resulting from an attack or attacks of lymphangitis in which the port of entry of the infection is known. This occurs as a result of infection often of superficial wounds, erosions of the toes or heels or by friction from shoes Post lymphangitic lymphedema may occur in patients with chronic ulcers of the feet, for example, varicose ulcers. Filariasis and tuberculosis produce post lymphangitic lymphedema (8).

Filariasis

This is a lymphedema which is caused by invasion of the lymphatic system by the worm Wuchereria bancrofti (8).

Etiology: The organism is carried by the mosquito and produces mechanical blockage of lymphatic vessels and lymph glands. The disease is endemic in certain areas and has been encountered during the war in Egypt and in the South Pacific (figure 394).

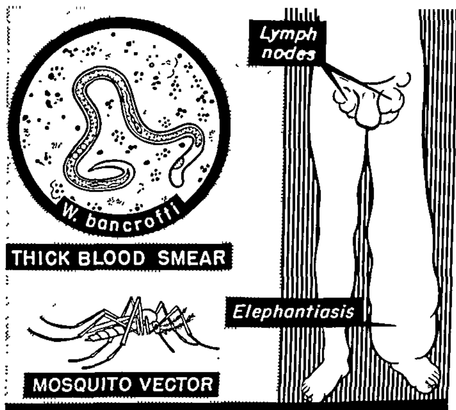


Figure 394. Filariasis, a secondary type of lymphedema.

Age, Sex and Race: All ages and races and both sexes may be affected.

History and Physical Examination: The disease is somewhat different in soldiers who were exposed to the infecting organism

for short periods of time than in the natives who had constant exposure. The soldiers usually suffered two or three mild attacks of lymphangitis which were transitory which did not leave a permanently swollen limb. The natives suffered repeated attacks with consequent blocking of almost all the lymphatics with persistent swelling of the limbs with elephantiasis which was characterized by a markedly swollen limb with thickened, hard irregular skin (9, 10).

Laboratory: It is possible but often difficult to find the parasite in the circulating blood. In the heavily infected cases the adult parasite may be found on section of the involved lymph nodes.

Treatment: This involves removing the patient from the infected area. Methods to eliminate mosquitos, dirt and overcrowding should be undertaken Local treatment consists of heat and elevation of the limb with compression bandages.

Tuberculous Lymphedema

This is lymphedema which is caused by the tubercle bacillus.

Age and Sex: This is most frequent in young women.

Etiology: Tuberculosis. The disease is associated usually with active glandular or pulmonary tuberculous lesions.

History and Physical Findings: Slow development of swelling of the legs usually occurs The swelling is nonpitting and usually involves the legs and thighs and is associated with tuberculous adenitis Swollen, tender lymph vessels often can be felt in the femoral or axillary region Cutaneous lesions of tuberculosis may be palpable in the middle or lower third of one or both legs

Treatment: Streptomycin has been employed for the disease with satisfactory results. Other antituberculous drugs should be used also

POST PHLEBITIC LYMPHEDEMA

This is an edema due to lymphatic obstruction and follows thrombophlebitis (5).

Pathogenesis: The edema appears as a result of lymphatic obliteration caused by a severe phlebitis often in the femoral or iliac region. *Occasionally severe periphlebitis* around the iliac vessels causes the lymphatic vessels and nodes to become fixed to

the wall of the vein. Occasionally ulcers, pain and trophic disturbances are present.

History and Physical Examination: The patient complains of swelling of the leg and pain along the course of the vein due to phlebitis. The edema involves often the body wall, thigh, leg and foot. Only the thigh may be involved at times. The edema is tense and is reduced only slightly by recumbency.

Differential Diagnosis: Post phlebitic lymphedema should be differentiated from post phlebitic venous edema as the latter characteristically involves the distal portions of the leg and is absent in the morning on arising after the patient has had a night's rest. Whereas the former may involve the entire leg and foot and does not disappear after rest in a horizontal position for twenty-four hours. After several days of elevation of the leg the edema may subside slightly in chronic cases

Treatment: Sympathectomy may be of slight value when ulcers are present, otherwise it is of little or no value. Roentgen therapy over the inguinal region is given using 100 r three times a week to a total of 1000 r. Radiation factors: killivolts 200, milliamperes, 7, filtration 0 5 mm copper, 1 mm aluminum, s d. 50 cm.

POST SURGICAL LYMPHEDEMA

Lymphedema occurs commonly after surgical removal of lymph glands associated with radical breast amputations for carcinoma of the breast (11, 13, 14). Conservative treatment should be carried out with elevation of the arm, heat and if necessary an elastic sleeve

NEOPLASTIC INVASION OF LYMPH NODES

This produces mechanical blockage of lymph nodes with resultant lymphedema. The upper extremity often is involved (12).

Etiology: This is usually caused by carcinoma of the breast or radical mastectomy. Tumor recurrence often causes the lymphedema which follows radical mastectomy for carcinoma of the breast. Other causes are burns, radiation, lymphangitis, venous thrombosis of the subclavian or axillary vein. Lymphedema secondary to the operative scar is possible.

Differential Diagnosis: When lymphedema is secondary to venous thrombosis the veins will be dilated and the venogram will show the block. The venous pressure is elevated often five times normal.

Treatment: Surgery, x-ray treatment, nitrogen mustard and prednisone may be of value.

LYMPHANGITIS

This may occur without lymphedema and be primary or secondary to infections and infestations, mechanical, chemical or physical irritation or to granulomata.

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CHAPTER 49

Tumors of Blood and Lymph Vessels

BLOOD VESSEL TUMORS

THE TUMORS of the blood vessel system are classified as benign and malignant.

BENIGN

The benign tumors are classified under the heading of: 1) hemangiomas, 2) glomus tumors, and 3) telangiectasia.

HEMANGIOMAS

BIRTH MARK

These are benign growths which are often present at birth and consist of vascular sinuses supported by a various amount of fibrous stroma. These tumors can be divided into the following types: 1) cavernous; 2) capillary, 3) plexiform; 4) sclerosing, and 5) various syndromes associated with hemangiomas (figure 396).

CAVERNOUS HEMANGIOMAS

These consist of masses of dilated, thin-walled vessels which are engorged with blood and may be localized or diffuse (1). The tumors are often present at birth or may appear shortly thereafter. Often the tumors are not seen easily as they may be deep in the tissues or may be small. After a few years the increased hydrostatic pressure from standing and walking makes these lesions become visible, especially when they are in the lower extremities.

Sex and Race: Both sexes and all races are involved

Etiology: These hemangiomas are considered developmental abnormalities of the vascular system.

Pathology: The tumors are composed of dilated, thin-walled



Figure 395. Giovanni Battista Morgagni, 1682 to 1771 He is considered to be the father of pathology He pursued the investigation of disease from its symptoms to the organ from which the symptoms arose.

pated. The tumor produces soft, poorly circumscribed, elevated red masses in or under the skin. The tumor shrinks slightly on elevation of the limb. Varicose veins may be associated. Usually arteriovenous fistulas are not present in which case the limb is of normal size, but when they are present, the limb may be enlarged and thrills and bruits may be present. When the tumor is localized very few symptoms are present. When it is diffuse there may be aching and a feeling of weight in the extremity. The localized form involves only one area such as the vertebra while the diffuse form may involve an entire limb.

Differential Diagnosis: Hemangiomas should be differentiated from varicose veins. The appearance of the hemangiomas at birth and a cyanotic discoloration of the leg are helpful in making the differentiation.

Laboratory: Biopsy of the tissues shows the typical, thin-walled endothelial lined, dilated vessels and arteriovenous fistulas may be present also.

Treatment: A variety of forms of treatment have been tried. Localized hemangiomas are treated successfully with radium, electrocoagulation, excision and by the injection of various sclerosing agents (1, 3). When these lesions are present on the face they should be treated by a competent plastic surgeon The treatment of the diffuse type is less satisfactory. Supportive elastic stockings may be helpful. Occasionally spontaneous arterial thrombosis occurs which causes the tumor to indurate.

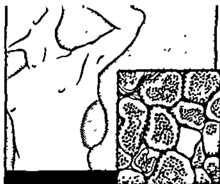
CAPILLARY HEMANGIOMA

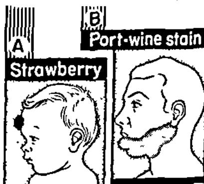
This is a common type of vascular tumor which may be present in a localized and in a diffuse form (1, 4). The localized form is referred to as a strawberry nevus while the diffuse form is called a port-wine stain. Both the localized and diffuse forms are similar except for the area covered by the lesion (figure 396).

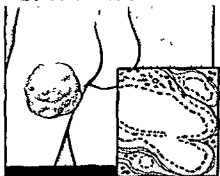
Age, Sex and Race: The disease appears at birth and is more common in females than in males. It involves all races.

Etiology: These are congenital in origin and probably represent an abnormal development from mesodermal tissue. The lesions are benign.

vessels and sinuses filled with venous blood which are lined with endothelium (2). The hemangiomas may be found on the face, neck, extremities, liver, bone (particularly in the vertebra), stomach, intestine, skin, subcutaneous tissue and muscle.







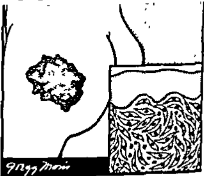


Figure 396. Various types of hemangiomas.

History and Physical Examination: Discoloration or enlargement of the part is noted at birth and the abnormality develops with age. When the tumor involves the extremities there is a cyanotic discoloration which appears as a mottling over the limbs. There is a sensation of reduced resistance when the tumor is pal-

capillary type with focal cavernomatous changes. Large angiomas may be present in the brain or spinal cord but only occasionally symptoms are produced by them.

VON HIPPEL-LINDAU DISEASE

This is a familial disease characterized by angiomas of the retina and cysts located mostly in the cerebellum (5). The meninges and spinal cord may be involved The symptoms resemble syringomyelia. Pancreatic cysts and renal cysts, as well as renal angiomas may be present. Pheochromocytomas may be associated with this disease. Pathologically the lesions consist of capillary and cavernous angiomas with or without thrombosis.

MAFFUCCI'S SYNDROME

This consists of dyschondroplasia with hemangiomas (7). The onset of symptoms is about the time of puberty. Males are involved more frequently than females. Dyschondroplasia occurs in the long bones and results in shortening of the bones and in fractures. Chondrosarcoma may develop. The hemangiomas may occur in the skin or in any part of the body or in the lips or palate. There is a tendency for phleboliths to form in the lesions.

GLOMUS TUMORS

These are tumors of the glomus body which may be classified according to the type of tissue which predominates in the histologic examination; these are 1) cellular; 2) neuromatous, and 3) angiomatous (figure 397).

History: Glomus tumors were described first by Wood. More exact knowledge was given by Barre (8).

Age and Sex: Glomus tumors occur at any age; however they are most common between twenty and fifty years of age. Males and females are affected in equal numbers.

Normal Glomus: These are found in the nail bed of the digits of man and in the skin of the hands and feet The glomus is a true arteriovenous anastomosis which connects an artery to a vein. The anastomosis is a serpiginous vascular structure which arises from an artery of small diameter and empties into a vein of larger diameter and is known as a Sucquet-Hoyer canal. It is

Pathology: The lesions are made up of many dilated capillaries with flattened endothelium.

History and Physical Examination: The complaint is usually that of a discolored area of the skin or a red growth on the skin. The localized form is an elevated, red nodule which resembles a strawberry. The diffuse form is a purple flat lesion with an occasional elevated nodule superimposed. Diffuse hemangiomas are most common on the face but they may involve the trunk or the extremities and are common in the occipital region. The lesion is not malignant. Premature development of varicose veins is common when the lesion involves the lower extremity. Arteriovenous fistulas may be present.

Treatment: This is similar to that described for cavernous hemangiomas.

PLEXIFORM HEMANGIOMA

This is a poorly circumscribed hemangioma due to extensive ramification of the blood vessels which often penetrate deeply into the surrounding tissues (5). These tumors may consist of the cavernous and capillary types or may be a mixture of the two (figure 396).

SCLEROSING HEMANGIOMA

This represents the end or involutional stage which occurs when the artery supplying a hemangioma becomes constricted usually by fibrous tissue which gives the lesion a superficial resemblance to a fibroma (figure 396).

STURGES-PARKES WEBER-DIMITRI SYNDROME

This is a neurocutaneous complex which consists of congenital angiomatoses of the skin and of the leptomeninges (5, 6). The skin lesions usually consist of *port-wine stains* which are limited to one side of the face or neck, although they may appear any place on the body or limbs. The meninges over the occipital, frontal, parietal or temporal lobes may be involved and be invested with dilated engorged veins Often calcific laminated concretions are present in the meninges so that the diagnosis may be suspected from the x-ray. The cutaneous angiomas are of the

open the anastomosis often is eight times the diameter of the artery from which it arises. Since the rate of flow varies with the fourth power of the diameter of the vessel a large amount of blood can be short circuited into the collecting veins without passing through the capillary bed. The anastomosis may at times close completely, forcing blood through the high resistance capillary channels. When the anastomosis is open there is a rise in venous pressure and skin temperature and arterial pulsations may be transmitted directly through the anastomosis into the venous side of the vascular tree.

Pathology: This varies depending upon whether the cellular, neuromatous or angiomatous elements predominate. By making serial sections the spot where the arteriovenous anastomosis enters the tumor may be demonstrated Non-medullated and medullated nerve endings have been located in close approximation to the epithelioid cells In the vicinity of the glomus Pacinian corpuscles may be present.

History and Physical Examination: Trauma initiates the symptoms in about 50 per cent of the patients. The pain is severe and progressive and varies with emotional disturbances, changes in position or temperature and often resembles the pain of causalgia. The pain may radiate from the extremity to the body and is most severe in the neuromatous type of lesion In the angiomatous type the patient may complain of increased temperature similar to that of a traumatic AV fistula With a small tumor localized pain over a small area (the size of a pinhead) may be present. The painful area can best be detected by touching various areas of the skin with the point of a pencil. These tumors are frequently located under the nail and thus pressure on the top of the nail may elicit pain. With large tumors the veins near the tumor may be dilated *The skin is warm and increased sweating may be present.* Although the lesions are especially common under the nail bed, they have been described in joints and in the corium. The tumor may grow under the nail externally tending to lift the nail or it may protrude internally and erode the bone. The size of the tumor does not exceed more than one centimeter in diameter in most cases (9).

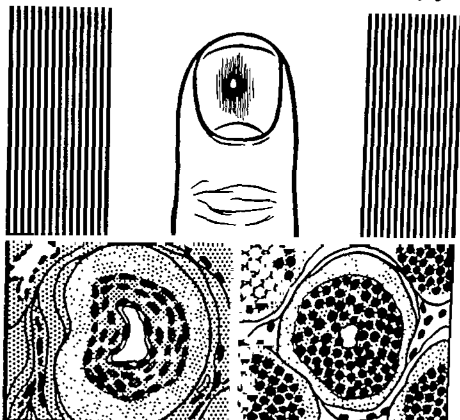


Figure 397. Clinical and pathologic findings in patients with glomus tumors

richly supplied by myelinated and non-myelinated (sympathetic) nerve fibers The neurovascular glomus consists of the arterio-venous connection, the connecting vein and artery and the loose surrounding tissue and its nerves. Histologically large polyhedral cells have replaced the normal media of the artery. These cells are referred to as epithelioid or glomus cells and are modified smooth muscle cells of the arterial wall. Elastic tissue is absent and there is no internal elastic membrane. When the glomus is

fingers, hands, eyelids, ears, scalp, pharynx, palate, neck or thorax. The lesions blanch when pressure is applied with a glass slide. The lesions bleed frequently.

Laboratory Work: A hypochromic anemia develops if bleeding is frequent. The white count, clotting time and clot retraction time are normal.

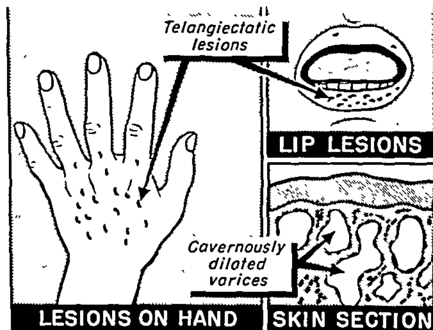


Figure 398. Rendu-Osler-Weber's syndrome A type of telangiectasia.

Diagnosis: The diagnosis is made because of the family history, the history of bleeding and the distribution of the lesions.

Differential Diagnosis: Purpura is differentiated because purpuric spots do not blanch with pressure from a glass slide. Hemophilia has a prolonged coagulation time. Aplastic anemia is characterized by a low platelet count, prolonged bleeding and clotting

Laboratory Tests: Erosion of bone may be present. The phalanx may be increased in length if the tumor develops early in life. The oxygen saturation of venous blood is increased. There is a rise in local venous pressure, venous blood temperature and venous blood oxygen. A blood pressure cuff inflated to just above the venous pressure and placed proximal to the tumor increases venous pressure and produces pain which may be extreme in the neuromatous type of lesion.

Treatment: This is by excision of the lesion. The lesions are not malignant and usually do not regrow after removal.

TELANGIECTASIA

Telangiectasia is a term which indicates a dilatation in a group of arterioles, venules or capillaries of the skin or mucous membranes. These may be congenital or acquired. A classification is as follows: 1) hereditary hemorrhagic telangiectasia; 2) spider nevi; 3) senile ectasia, and 4) simple telangiectasia.

HEREDITARY HEMORRHAGIC TELANGIECTASIA

Rendu-Osler-Weber's Syndrome

This is a syndrome which is usually familial consisting of telangiectatic lesions of the skin and mucous membranes which have a tendency to bleed (figure 398).

History: The disease was described by Rendu in 1896 and was redescribed by Osler and later by Weber (10, 11).

Age, Sex and Race: The disease often appears at an early age. There is no sex predilection and all races are affected.

Etiology: The lesions appear to be inherited as a dominant trait.

Pathology: Grossly the lesions are flat or slightly raised irregular red spots which vary from 2 to 3 mm in diameter. Microscopically the lesions consist of thin walled dilated capillaries which lie immediately beneath a thin epidermis. The capillaries consist of a single layer of endothelial cells.

History and Physical Examination: During early life there is a tendency toward frequent nose bleeds which are due to lesions in the nasal mucous membranes. Later in life these lesions may involute but new lesions appear on the tongue, face, lips, cheeks,

SENILE

These are small, bright, red-purple areas which frequently appear on the face or anterior trunk of elderly individuals. They are about 5 to 10 mm in diameter and consist of dilated capillaries. They are of no clinical significance and may be removed by destruction of the lesion; however treatment usually is not necessary.

SIMPLE

These are dilated capillaries often resulting from exposure to sun, wind, heat, radiation or x-rays. They may be secondary to venous insufficiency. Treatment may be carried out for cosmetic reasons in which case the capillary may be injected with sodium morrhuate. This should be done carefully and by one experienced in the field so that pigmentation is not produced.

MALIGNANT

The malignant tumors of the blood vascular system are hemangioendotheliomas, hemangiosarcomas and Kaposi's sarcoma.

HEMANGIOENDOTHELIOMA

These are vascular tumors which result from malignant proliferation of endothelial cells. The cells may grow and metastasize slowly or rapidly (13)

Age, Sex and Race: All ages, races and both sexes are involved.

Etiology: Malignant proliferation of the endothelial cells

Pathology: Microscopically the tumor consists of large, pale malignant endothelial cells which are closely packed. The cells may exist in cords. Newly formed blood vessels may be present.

History and Physical Examination: *The lesions may occur in* the skin as solid, elevated noncompressible purple-red tumors The lesions may occur anywhere in the skin and subcutaneous tissue and vary from one to five cm in diameter. Mucous membranes may be involved. Smaller lesions may occur around the main lesion Lesions in the gastrointestinal tract are not unusual. These lesions may involve bone (Ewing's tumor) (1, 14).

times and a history of anemia which antedates the hemorrhages with aplasia of the bone marrow. Hypoprothrombinemia is differentiated because of the low prothrombin time.

Treatment: This consists of destroying the lesion with electrocoagulation, radium, cautery or chromic acid. When acute bleeding is present epinephrine may temporarily stop the bleeding. For acute epistaxis a finger cot tied around a catheter may be employed by the patient. The finger cot, lubricated with petroleum jelly, is placed in the nose and the catheter in the mouth. The patient blows into the catheter which produces pressure on the bleeding area in the nose. Large doses of estrogens may be tried.

SPIDER

These are cutaneous, dilated arterioles which take the form of a star and are associated often with liver disease (12) (figure 296).

History: Spider telangiectasia were first described by Wilson in 1865. They are also called spider hemangiomata.

Age, Sex and Race: All ages and races and both sexes may be involved.

Etiology: The lesions may be congenital or acquired. The congenital lesions are without significance while the acquired lesions are associated with pregnancy and liver disease or may be idiopathic.

History and Physical Examination: Usually arterial spiders do not produce symptoms. They occur especially on the face, neck and upper part of the arms and chest. They rarely appear on the lower extremities. Often they appear suddenly and fade quickly. There is a tendency for the lesions to appear in crops. The lesions tend to pulsate and they can be blanched by pressing on the head of the lesion. On release of pressure the blood flows from the hub or central point to the periphery.

Treatment: Usually no treatment is required. However destruction of the lesion with chromic acid or electrocoagulation could be carried out. When associated with liver disease treatment of the underlying disease process is important.

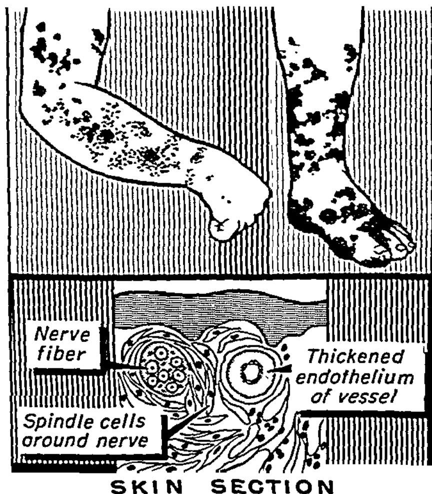


Figure 399. Clinical and pathologic findings in patients with Kaposi's sarcoma.

Pathology: A variety of histologic pictures is seen. There is hemorrhage into the skin and infiltration with the lymphocytoid cells of Marchand. There is proliferation of vascular endothelium and formation of new capillaries with infiltration of lymphocytes

Prognosis: Usually the degree of malignancy is low; however the lesions spread and metastasize.

Treatment: When metastasis is absent surgical excision is possible and x-ray therapy may be applied. Many of the tumors are x-ray sensitive. Ultimately amputation may be necessary.

HEMANGIOSARCOMA

These are blood vessel tumors in which fibroblastic connective tissue and vascular tissues are involved.

Age, Sex and Race: All ages and races and both sexes are involved.

Etiology: The lesion may follow *irradiation following mastectomy.*

History and Physical Examination: The history may be that of mastectomy followed by irradiation, then tumor formation which consists of soft, bluish red nodules surrounded by smaller nodules. Occasionally the lesions occur without previous irradiation. Thrills may be felt over the tumors and bruits may be heard. Pulsations may be present.

Laboratory Work: Biopsy shows proliferation of the connective tissue of the blood vessels.

Prognosis: This is poor. The lesions grow rapidly and metastasize early (15).

Treatment: Wide excision of the lesion is made if metastases have not occurred. X-ray irradiation may be helpful; however it is not curative.

KAPOSI'S SARCOMA

This is a malignant neoplasm involving blood vessels which is *characterized by subcutaneous nodules and visceral lesions* (figure 399).

History: The disease was first described by Kaposi in 1872 (16).

Age, Sex and Race: The disease commonly affects adults. It predominates in Hebrews and Italians, is rare in American Negros but is common in the Bantu. Ninety-five per cent of the patients are males. Eighty per cent of the patients range from forty to seventy years of age; however the disease may be seen before the age of twenty.

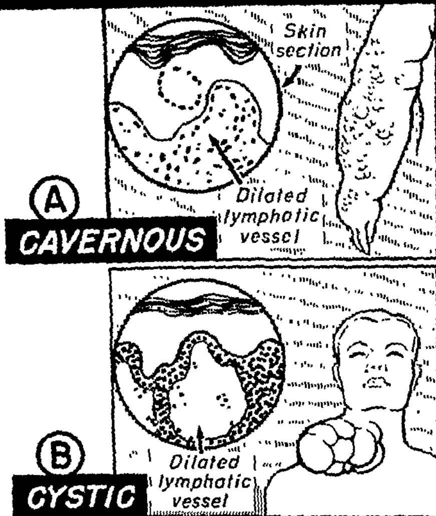


Figure 400 *Clinical and pathologic findings in patients with lymphangioma of the cavernous and cystic types*

CAVERNOUS LYMPHANGIOMA

These tumors are present usually at birth and grow slowly thereafter (figure 400). Often these lesions are found in associa-

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tion with hemangiomas. Microscopically dilated lymphatic vessels are present which are filled with lymph. The contents of the vessel often contain lymphocytes and endothelial cells. The tumors are common in the skin and subcutaneous tissue and may be one or two cm in diameter or may greatly exceed this. The lesions are common on the extremities, in the mouth, on the tongue, eyelids, groin, thighs and back. Aspiration of the lesion reveals lymph which often is present in large quantities. Often the lesions appear as numerous vesicles which are thick walled and about five mm in diameter. Bacterial infections are common. Usually these are treated by surgical excision; however keloid formation and recurrence is common. X-ray irradiation or radon seed implantation has been carried out.

Cystic Lymphangioma Hygroma

These are congenital lesions commonly occurring in the neck which grow rapidly (figure 400). They consist of distended lymph vessels lined with endothelium which contains serous fluid or lymph. They may occur in the axilla, groin, retroperitoneal space, pelvis or thoracic wall. The tissues transilluminate well *and are easily compressed. Infection is common and when it* occurs it is serious. Treatment is usually surgical excision because the tumors are relatively resistant to x-rays and radium. Injection with two ml of sodium morrhuate has been carried out to produce sclerosis of the tumor (13).

MALIGNANT

A malignant tumor of the lymph system is the lymphangiosarcoma.

Lymphangiosarcoma

These are malignant tumors which often follow mastectomy and radiation or radiation alone (18).

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CHAPTER 50

Treatment of the Peripheral Arterial Diseases

THE TREATMENT of the peripheral arterial diseases varies to a certain extent with the etiology of the disease; however certain therapies are indicated in the arterial diseases of a variety of etiologies, e.g., the vasodilating procedures are indicated in the therapy of arteriosclerosis, thromboangiitis obliterans, frostbite, ergotism and other disease states. In order to determine rapidly the effectiveness of a specific drug or therapeutic procedure in a specific patient a plethysmographic examination can be carried out which allows a quick evaluation of the therapy to be made. Treatment procedures are medical and surgical.

MEDICAL TREATMENT

Medical treatment consists of 1) general care and protective measures, 2) drug therapy and 3) physical therapeutic procedures.

GENERAL CARE

The patient should dress warmly and keep the room and environment warm. The diet should be low in fat and high in protein. A low fat diet is employed because of the association of certain peripheral arterial diseases with high blood fat levels The unsaturated oils such as corn oil may be employed as they do not raise cholesterol and may lower it. A high protein diet is employed because of the high specific dynamic action of protein which increases the circulation to the extremities. Previous studies have shown that the amino acids are important in increasing the peripheral blood flow (1, 2). Careful control of carbohydrate intake and total calories should be employed in patients with vascular disease due to diabetes mellitus. Vascular exercises should be performed with the feet horizontal for ten minutes followed by

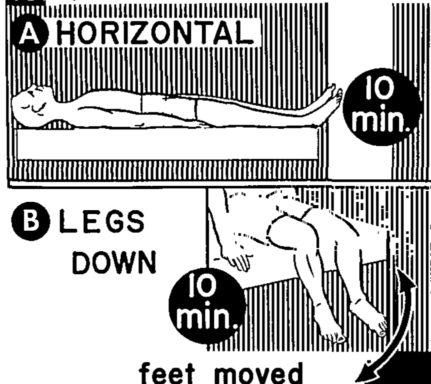


Figure 401 The legs are horizontal for about ten minutes (A) and then dependent for about ten minutes (B) Exercises of this type are preferable to conventional Buerger's exercises in which the feet are elevated because of the ischemia which the elevation produces

the foot-down position for an equal length of time (figure 401). The foot-up position should be avoided as in this position blood must flow against gravity which is detrimental to the tissues (3). The head of the bed should be elevated on four inch blocks so that the blood flow is toward the foot at all times. A firm mattress should be used so that the buttocks do not sag as sagging results in a relative foot-up position Massage of the limbs and sunburn

✓ are to be avoided. The patient should not cross his legs for long periods of time nor should he use strong medicated salves on the legs and feet without proper advice. He should walk to the point of pain and then stop until the pain leaves after which he may walk again. The shoes should be large, soft and produce no pressure on the feet. Arch supporters if employed should be soft and carefully fitted to avoid irritation. The feet should be washed daily with tepid water and a bland soap. Soaking of the feet in water especially if the water is hot is undesirable. *Wet soaks tend* to produce cooling by evaporation and are generally to be avoided. Soft white cotton stockings which are smooth should be worn next to the skin and woolen stockings may be worn over the cotton *stockings when additional warmth is required. Direct heat to the* legs by hot water bottles, electric pads or heat lamps is to be avoided as burning of the tissues may occur because blood flow in an ischemic limb often is not great enough to remove heat adequately. *Athletes' foot is to be avoided by changing the socks* daily and applying appropriate foot powder when necessary.

DRUGS

The drugs useful for treating peripheral vascular disease are the: 1) antibiotics; 2) anticoagulants, 3) decalcifying agents; 4) hormones; 5) locally acting agents; 6) muscular depressants; 7) proteolytic agents; 8) steroids; 9) vasoconstrictors; 10) vasodilators; 11) positive inotropic agents; 12) vaccines and antitoxins, and 13) vitamins.

Antibiotics

Penicillin, streptomycin, tetracycline and other antibiotics have specific indications and are selected on the basis of cultures made from ulcerated or other lesions when possible (4, 5). Penicillin is effective against gram positive organisms including anerobes and spore bearing forms Streptomycin is effective against many gram negative organisms and against certain gram positive organisms as well (staphylococci and aerobic streptococci). When the organism has not been identified penicillin and streptomycin may be employed together to obtain a wide spectrum of activity. Oxy-

tetracycline (Terramycin®) is an effective, wide spectrum antibiotic which attacks gram positive bacteria including the aerobes, anerobes, spore bearing and non-spore bearing organisms and certain gram negative bacteria. Antibiotics employed locally will be discussed under the heading of locally acting agents.

ANTICOAGULANTS

Indications: The anticoagulants are of value in the treatment or prevention of arterial or venous thrombosis, arterial embolism, mural thrombi occurring in patients with heart disease, trauma to vessels, frostbite, crush injuries, pulmonary emboli, phlebothrombosis and thrombophlebitis (6).

Contraindications: Anticoagulants are contraindicated generally in patients with an abnormality of the clotting mechanism, vitamin K or C deficiency, liver disease, late pregnancy, renal disease, pulmonary tuberculosis, hemophilia, purpura, hemorrhages, blood dyscrasias, recent peptic ulcer, fresh abraded wounds, after operations for jaundice, when draining wounds are present, when there is inadequate hemostasis, with diseases of the lung or brain, in patients with subacute bacterial endocarditis, with severe hypertensive disease, toxemia of pregnancy, dissecting aneurysms of the aorta or when reliable laboratory tests are not available.

Long Term Therapy: This is carried out in patients who are in constant danger of emboli or of venous or arterial thrombosis. Patients with advanced arterial obstruction with sluggish blood flow or with atrial fibrillation, migrating thrombophlebitis, previous mesenteric thrombosis and arterial emboli are candidates for long term therapy

Types of anticoagulants: These are of two major types; the heparin and heparin-like agents which alter the coagulation time and the coumarin and the indandione derivatives which alter the prothrombin time (6, 7, 8, 9) (figure 402).

ANTICOAGULANTS AFFECTING COAGULATION TIME: The drugs which affect the coagulation time are heparin, Paritol and thrombocid.

Heparin: Jay McClean in 1916 discovered this agent and it was synthetized by Howell in the same year. Heparin is a sulfurated polysaccharide containing glucosamine, a uronic acid and sulfuric

Characteristics of Several Commonly Used Anticoagulants

Drug	*Initial Dose, Mg*	*Maintenance Dose, Mg/Day*	*Time of Onset of Action, Hrs*	*Peak Effect, Days*	*Recovery of Prothrombin or Coagulation Time After Stopping Drug, Days*	*Antidote*
Heparin	75 mg IVI 100 mg SC	200 SC	1/4	1 hr	4 hrs after IV 12 hrs after SC	Protamine sulf. Transfusion Toluidine blue
Dicoumarol Dicumarol ®	1st day 300 2nd day 200	50–100	36	3	5	K_1 or K Transfusion
Ethyl biscoumacetate Tromexan ®	1500–1800 Divided	600–900 Divided	18	1	2	K_1 or K Transfusion
Warfarin Coumadin ®	65 IVI 85 oral	12.5 oral	12–24 hr, IV 24 oral	2 after Oral	4	K_1 or K Transfusion
Phenprocoumon Marcumar ®	1st day 24 2nd day 9	3	24	2	5	K_1 or K Transfusion
Cyclocoumarol Cumopyran ®	1st day 100–200 2nd day 75	12.5–50	24	2	5	K_1 Transfusion (K not effective)
Phenindione Danilone ®	200–300	25–100	18	2	3	K_1 Transfusion (K not effective)
Diphenadione Dipaxin ®	1st day 24–30 2nd day 10–15	3–5	48	3	7	K_1, K Transfusion
Acenocoumarin Sintrom ®	20 orally	8–12	24	1/2 to 2	2–3 days	K_1 or K Transfusion

Figure 402. Table showing characteristics of several commonly used anticoagulants.

acid esters (10, 11). The exact structural formula is not known. It is derived from animal sources such as beef lung and liver. It is thought that heparin is formed in the mast cells which are numerous in the perivascular connective tissue.

Mode of Action: Heparin has an almost immediate effect upon the clotting mechanism and acts as an antagonist to the thromboplastin derived from the platelets By interaction with the labile factor heparin interferes with the conversion of prothrombin to thrombin. Heparin also forms an antithrombin with serum albumin which prevents thrombin from reacting with fibrinogen to form fibrin.

Duration of Action: Heparin has a rapid onset of action when given intravenously and much of the drug is excreted by the kidneys. *The method of administration influences the duration of* action greatly. After intravenous administration of a therapeutic dose there is an effect in fifteen minutes which lasts approximately four hours. When given subcutaneously the duration of action is about twelve hours. Also the duration is related to the size of the dose administered. When 10 mg is given intravenously the duration is forty-five minutes, while 50 mg last three hours. When given intramuscularly the duration of the effect is about the same as when given intravenously.

Dose: The total twenty-four hour dose is about the same regardless of the route of administration. The total twenty-four dose is calculated on the basis of body weight For a 100 pound subject 200 mg is given, 150 pound subject 250 mg and 200 pound subject 300 mg

Methods of Administration: Heparin may be administered subcutaneously, intravenously or intramuscularly.

Subcutaneous Administration· This method is preferred by many and has the advantage of infrequent injections. The total twenty-four dose is divided in half and the injection is made deeply subcutaneously every twelve hours. Usually a coagulation time is obtained before every other injection. A highly concentrated solution is employed which contains 200 mg per cc. The injection is made in the subcutaneous fat over the iliac crest so that an intramuscular injection is avoided A three-quarter inch #25 needle is employed, and injections are made while the needle is

being withdrawn. In this way a track of concentrated heparin is laid from which absorption occurs. The coagulation time should be about two times normal (20 minutes).

Intravenous or Intramuscular Administration: The total twenty-four hour dose is calculated on the basis of body weight as described above and is divided and administered every four to six hours. A coagulation time should be performed just prior to an injection each day, and the time should be approximately two times normal (20 minutes). The blood heparin level with either intravenous or intramuscular injection is high about an hour after the injection and low just prior to the next injection.

Depot Technique. Depo-Heparin Sodium® may be given every eighteen to twenty-four hours. The dose is 200 mg and may be administered with or without a local vasoconstrictor. The coagulation time should be checked at twelve and twenty-four hours to determine the effect. The second injection is given when the coagulation time is two times normal (20 minutes).

Continuous Intravenous Therapy: This is used only rarely because of the continuous nursing care which is required. The total twenty-four dose is calculated on the basis of body weight and the rate of drip adjusted so that the coagulation time is at all times two or three times normal (20 to 30 minutes).

Advantages of Heparin: The rapid onset of action is desirable, especially when surgery is contemplated and the action of the drug can be stopped quickly if desired by employing injections of Protamine Sulfate®.

Side Effects: Anaphlyaxis has occurred on intravenous injection Therefore the drug should be given slowly when it is given by this route. Subcutaneous or intramuscular heparin may cause pain, swelling, tenderness, fever and in rare instances a slough at the site of the injection.

Control of Hemorrhage: Hemorrhage can be controlled by Protamine Sulfate®. Five cc of 1 per cent solution is administered intravenously and is repeated every one to four hours as needed. Also whole blood transfusions using fresh blood or plasma may be employed and has a more lasting effect than does Protamine®. A derivative of toluidine blue, *tolonium chloride sulfate* (Blutene®) produces a prolonged coagulant effect (12). The oral dose

is 100 mg three times a day but the drug may be given intravenously as well (figure 403). At times it may be desirable to demonstrate the presence of heparin or heparinoid substances in the blood which is done by titrating the blood with Protamine Sulfate® as follows:

1. Add exactly 0.05 cc of Abbott Heparin Sodium® solution, 1000 U.S.P. units per cc to a clean 10 cc vial or bottle and allow it to dry spontaneously. (The heparin is relatively stable and will retain its potency for several months.)

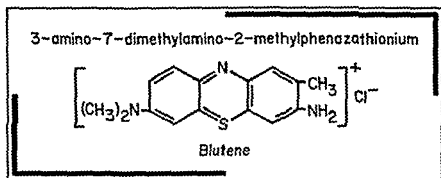


Figure 403 Formula of Blutene which is employed for controlling hemorrhage resulting from heparin

2. Add 5 cc of freshly drawn whole venous blood carefully to the five cc mark of the previously prepared heparin vial by placing the needle against the bottom of the vial and depressing the plunger.

3. Invert the stoppered vial 15 times.

4. Add 0.7 cc of a 0 1 per cent solution of Protamine Sulfate with a graduated 1 cc pipette (1 per cent Protamine Sulfate Solution, Lilly, containing 0 25 per cent phenol, diluted 1:10).

5. Invert the vial again 15 times and let stand for 20 minutes.

6. Make reading in direct light. If blood is clotted and remains so on inversion of the vial, the test is negative and a clotting defect is not present. If blood is fluid the test is positive and a defect is present.

Paritol and Thrombocid: These are injectable heparin-like drugs which prolong the coagulation time. However both pro-

duce undesirable side effects. Paritol has produced swelling of the extremities and vascular collapse while Thrombocid has produced partial or complete transient alopecia.

ANTICOAGULANTS AFFECTING THE PROTHROMBIN TIME: These are dicoumarol, ethyl biscoumacetate (Tromexan®), warfarin (Coumadin®), cyclocumarol (Cumopyran®), phenindione (Danilone®), phenprocoumon (Marcumar®), acenocoumarin (Sintrom®), and diphenadione (Dipaxin®).

Bishydroxycoumarin; Dicoumarol (Dicumarol®) (figure 404) (9, 13, 14): This agent unlike heparin is effective only in vivo.

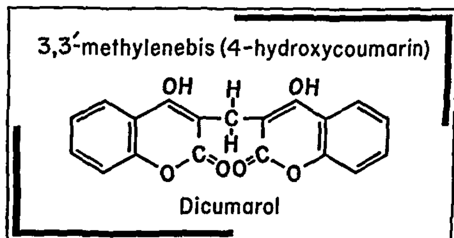


Figure 404. Formula of dicoumarol which is employed as an anticoagulant.

It interferes with the synthesis of prothrombin in the liver. Dicoumarol decreases the stable factor and diminishes the concentration or alters the molecular structure of prothrombin in the plasma. In therapeutic amounts it produces a reversible functional change in the liver so that withdrawal of the drug is followed by gradual restoration to normal. Other liver functions are unaltered. The agent is readily absorbed into the blood stream and is distributed in the liver, lungs, kidneys and other tissues after which it is metabolized or redelivered into the plasma but is not excreted in the urine. The average rate of disappearance from the plasma is from 15 to 20 per cent a day. All patients do not respond to the drug in the same way. Therefore the dosage must be individual-

ized. The usual dose for an average man is 300 mg the first day and 200 mg the second day. On the third day the drug may be given according to the prothrombin test (figure 405). The ideal prothrombin concentration is 20 to 30 per cent. The average maintenance dose is 50 to 100 mg a day although this must be determined by frequent prothrombin tests. Vitamin K_1 (Mephyton®) and vitamin K in relatively large amounts counteract the

DOSAGE SCHEDULE

PROTHROMBIN Concentration %		DICOUMAROL Mg.
0 - 10		0
11 - 20		25
21 - 30	*Ideal level*	50
31 - 40		75
41 - 50		100
51 - 60		125
61 - 70		150
71 - 80		175
81 - 90		200
91 - 100		225

Figure 405 Typical dicoumarol schedule which is employed after one or two large initial doses. The schedule may have to be changed if dicoumarol sensitivity or resistance is encountered

inhibitory effects of dicoumarol upon prothrombin liberation. The dose of Mephyton® is 50 to 150 mg intravenously followed by repeated injections or by oral medication in doses of 5 mg six times daily.

Ethyl Biscoumacetate (Tromexan®) (figure 406) (15): This agent is approximately 1/5 as potent as dicoumarol on a milligram basis and has the same mode of action. Individual differences in

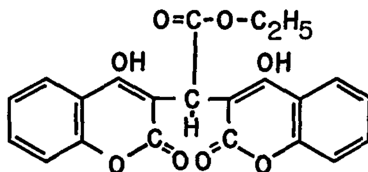


Figure 406. Tromexan, an anticoagulant which prolongs the prothrombin time.

sensitivity to Tromexan® are similar to those noted with dicoumarol. The correct dosage must be established on the basis of frequent prothrombin tests. The agent begins its action in about eighteen hours. The effect ceases two days after administration is stopped. An initial twenty-four hour dose of 1500 to 1800 mg is given with a daily maintenance dose of 600 to 900 mg. Because of the rapid metabolism of the drug the dose should be given in

divided amounts throughout the day. The prothrombin time is lowered quickly and toxic effects may be controlled with large doses of Vitamin K_1 (Mephyton®).

Warfain, Sodium (Coumadin®) (figure 407) (16): This agent is effective orally and parenterally and has a mechanism of action which is similar to dicoumarol. After intravenous injection the prothrombin time is lowered in from twelve to twenty-four hours

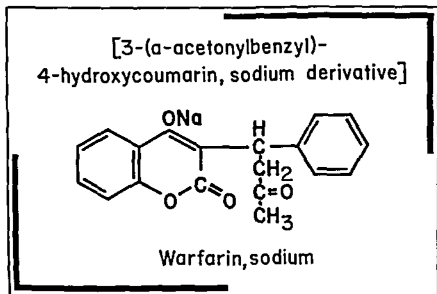


Figure 407. Warfarin, an anticoagulant which prolongs the prothrombin time

and the effect lasts four days. The intravenous dose is 1 mg per kilogram of body weight which is about 65 mg for an average size patient. The minimum intravenous dose is 50 mg and the maximum dose for patients over 80 kilograms is 75 mg. Subsequent intravenous doses should equal $^2/_3$ of the initial dose and should be given when the prothrombin concentration starts to fall. After an initial intravenous dose, subsequent administration can be oral in doses of 12.5 mg daily. After an oral dose an effect is present in twenty-four hours and the duration is about four days. For initial oral administration the dose is about 85 mg (range 75 to

100) which has an effect lasting up to four days. Subsequent oral doses follow the same schedule as after an initial intravenous dose. The dose should be reduced for patients after surgery or with vomiting as they are more susceptible to the agent. Coumadin® is soluble in water, effective in small doses and the initial hypoprothrombinemia appears earlier than with dicoumarol. It has few side effects and the hypoprothrombinemia is readily counteracted with vitamin K_1 (Mephyton®) or K. The intravenous route of administration eliminates the variability in blood levels resulting from differences in absorption.

Acenocoumarin (Sintrom®) (17): This agent has an average starting dose of 20 mg orally with a range of 12 to 18 mg. The average maintenance dose is 8 to 12 mg daily. Hypoprothrombinemia usually begins within twenty-four hours after the initial dose, the peak effect is one-half to two days. The prothrombin time returns to normal two to three days after the drug is stopped. This agent has a wide margin of safety. However regular prothrombin determinations should be made to avoid accidental overdosage. The antidote is vitamin K_1 (Mephyton®) and vitamin K. When an immediate anticoagulant effect is desired heparin may be used simultaneously.

Phenprocoumon (Marcumar®) (18): This is a potent oral anticoagulant and has a time of onset of twenty-four hours and reaches a peak effect in two days. The prothrombin time returns to normal five days after the drug is stopped. The oral dose on the first day is 24 mg (21 to 30). A twenty-four to forty-eight hour prothrombin test is taken before additional medication is given and subsequent doses depend upon the prothrombin concentration. On the second day usually 9 mg is administered. The maintenance dose is 3 mg (1.5 to 4.5 mg daily). This agent must be given cautiously as an overdose of 0.5 mg for a few days may lead to an abnormal prothrombin level and to hemorrhage.

Cyclocoumarol (Cumopyran®) (figure 408) (19): This is a synthetic anticoagulant related to dicoumarol. Compared with dicoumarol the action takes place more quickly and it lasts for a longer period of time after the drug has been stopped. Therapeutic levels have been maintained by giving the drug orally every two to three days. The first dose is from 100 to 200 mg orally.

Therapeutic effects are reached in twenty-four hours. The second dose is 75 mg. If the prothrombin test is less than 30 per cent concentration a daily dose of from 12.5 to 50.0 mg is given. Smaller doses are employed with cardiac decompensation or after myocardial infarction. The hypoprothrombinemic effect cannot be reversed by vitamin K; however, vitamin K_1 (Mephyton®) 50

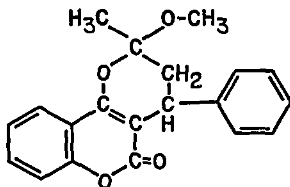


Figure 408 Cyclocoumarol, an anticoagulant which prolongs the prothrombin time.

to 150 mg intravenously or orally in doses of 5 mg six times a day is effective.

Phenindione (phenylindandione) (Danilone®), (Hedulin®), (Indon®) (20): This is a synthetic anticoagulant which is not related chemically to dicoumarol but which has a similar mode of action in that it acts by lowering the prothrombin time. An ad-

vantage is a rapid onset of action and low cost. The disadvantage is that a small percentage of patients develop albuminuria, allergic manifestations, agranulocytosis or are resistant to the agent. The onset of action occurs 18 hours after an initial dose. The maximum effect occurs in two days and the prothrombin concentration returns to normal three days after cessation of administration. The oral dose is 200 to 300 mg initially in divided doses according to body weight in the first twenty-four hours. Half of the drug is given in the morning and half at night. The prothrombin concentration is determined daily and the dose is individualized according to the response. The maintenance dose is between 25 and 100 mg a day. The hypoprothrombinemia is not counteracted by vitamin K but is counteracted by large doses of vitamin K_1 (Mephyton®).

Diphenadione (Dipaxin®): Therapeutic levels are usually reached in forty-eight hours after the initial dose. The action may persist for seven days after discontinuing the drug. Before the drug is given a prothrombin test is run to be sure that it is normal. On the first day 24 to 30 mg is given and on the second day 10 to 15 mg is given. At the end of forty-eight hours if the prothrombin concentration is less than 20 per cent (Quick) the dosage is discontinued until the prothrombin starts to decrease. The daily maintenance dose is 3 to 5 mg and should be adjusted to maintain the prothrombin concentration between 20 and 30 per cent. For an immediate anticoagulant effect diphenadione may be used with heparin. Frequent prothrombin times are essential to prevent accidental bleeding. Periodic blood tests should be carried out because of the rare possibility of agranulocytosis.

Combined Dicoumarol and Heparin Administration: Dicoumarol and heparin often are employed together. Heparin is used because of its rapid action and dicoumarol for maintenance therapy. The following technique is satisfactory. Blood is drawn for a prothrombin test before either dicoumarol or heparin is started and daily prothrombin times are determined being sure that blood is drawn as long as possible after the heparin injection, as heparin in large doses alters the prothrombin time. The first heparin dose is 75 mg intravenously, and at the same time a subcutaneous injection of heparin is given. The twenty-four hour

dose is calculated on the basis of the body weight. Subcutaneous injections of concentrated heparin are given every twelve hours, and the coagulation time is maintained at twenty minutes by increasing or decreasing the dose. On the second day 200 mg of dicoumarol is given The prothrombin test is kept between 20 and 30 per cent concentration if possible. On the third day the dicoumarol chart is followed (figure 404) to regulate the dosage. Heparin is discontinued when the prothrombin concentration is 30 per cent or if the coagulation time is unduly prolonged.

Treatment of Hemorrhage: Hemorrhage from the coumarin and indandione derivatives is best treated with repeated doses of vitamin K_1 (Mephyton®) (figure 409) in doses of 50 mg diluted

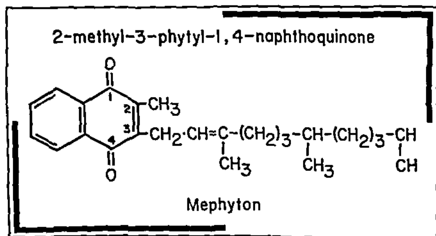


Figure 409. Vitamin K1 which may be employed for the treatment of hemorrhage due to anticoagulants which prolong the prothrombin time

in 9 cc of sterile distilled water and injected over a period of ten minutes (21). This may be followed by transfusions of fresh whole blood Blood which has been stored for more than twenty-four hours is not satisfactory because of breakdown of plasma protein Transfusions must be repeated frequently because of the long duration of action of the coumarin derivatives. Mephyton® 5 mg orally every four hours may be employed but the action is slow. The vitamin K preparations are less effective than vitamin K_1 However 75 mg of vitamin K (Synkavite® or Hykinone®)

intravenously repeated at four hour intervals for three or four doses for three days shortens the length of the hypoprothrombinemia and is useful when the prothrombin concentration is lower than is desired.

Decalcifying Agents

Ethylene diamine tetra-acetic acid (Disodium Versenate®): This is a synthetic chelating agent which forms strong soluble complexes with cations in solution especially alkaline earths. The drug has been employed for removing calcium in patients with scleroderma. It has been shown by Clarke, Clarke and Mosher that the drug is capable of reducing the amount of calcium in the kidneys of patients with nephrocalcinosis (22). Two and one-half grams of the agent in 500 ml of normal saline are given intravenously daily for six weeks or more. Side effects are nausea and thrombophlebitis while overdosage produces tetany and hemorrhage because of its anticoagulant action.

Hormones

Relaxin (Releasin®): This is a hormone of pregnancy which acts on the connective tissue of the symphasis pubis of the guinea pig, allowing softening of the joint tissue to occur at the time of delivery of the young. The softening results from depolymerization of the ground substance of the tissues (23). The agent is present in the blood of women during pregnancy, and it disappears from the blood within twelve hours after delivery (24) The hormone is a protein derivative with low molecular weight. It has been employed with estrogens in scleroderma to soften tissues, and it has been reported that increased mobility of the joints occurs The usual treatment is as follows: The conjugated equine estrogen (Premarin®) is given in doses of 1.25 mg daily for two months After two weeks of therapy Releasin® is given in doses of 20 mg daily intramuscularly for six weeks or more. The two drugs are employed together because of results observed in animals. Various groups working independently have reported encouraging results in scleroderma with this therapy. However, a large series of patients has not been treated.

LOCAL AGENTS

Fungicides: Calcium undecylenate (Desenex®) ointment and powder may be applied to the feet for athletes foot. Propionate-caprylate (fatty acid) compound (Sopronol®) also is effective and may be employed as an ointment, powder or solution. Solutions of potassium permanganate 1:10,000 as soaks may be used if these agents fail.

Bacteriostatic Local Agents: Topical antibacterial therapy is employed after necrotic tissue is removed with the aid of soaks or proteolytic agents, and contact between the drug and the infecting organism is established. Continuous application of antibacterial agents is accomplished as follows: Sterile gauze is cut to the size of the ulcer and placed over it One or two catheters are placed on the gauze and are used to convey an appropriate bacteriostatic agent to the gauze and to the wound. The catheters are covered with more gauze and a rubber sheet. This dressing is left in place for three days. Every four hours, 2 or 3 ml of a bacteriostatic or antiseptic solution is injected into the catheters. Cultures are made every three days, and drugs are tested for their bacteriostatic effect on the organism to determine the most suitable drug to employ.

Azochloramid®: This is used for the removing of eschars from ulcers and for the treatment of stasis ulcers. The normal skin around the lesion is covered with sterile petroleum jelly for protection. Gauze saturated with Azochloramid® cut to the size of the ulcer is placed over the ulcer. This is observed twice daily and removed when the eschar is soft.

Penicillin: This is effective locally, 1000 units of aqueous penicillin per cc and is used when infections are caused by pure or mixed strains of gram positive, penicillin-sensitive organisms.

Bacitracin: This is useful for gram positive bacitracin sensitive [illegible]

cent and 200 units of streptomycin per cc has been found effective for infections containing both gram positive and gram nega-

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Neomycin: This is an ointment containing 5 mg per gram or a solution containing 1 to 5 mg per cc and is effective against gram negative organisms or against mixed infections.

Nitroglycerin Ointment (Nitroglan®): This has been applied locally to the skin of the digits for producing vasodilatation (26). After application the skin temperature increases 2 to 3 degrees. It is indicated in patients with Raynaud's disease, frostbite and various vasospastic states.

Muscular Depressants

Quinidine Sulfate, 0 2 gram (3 grains) with the evening meal and 3 grains before bed is useful for preventing night cramps.

Quinine 0.6 gram (10 grains) is used for night cramps.

Benadryl is an indirect muscular depressant as it is to some extent anticholinergic. Fifty mg at night assists in the prevention of night cramps.

Proteolytic Agents

Proteolytic enzymes have been suggested for the treatment of ulcers of arterial and venous origin.

Streptokinase and Streptodornase in a ratio of 3 or 4 to 1 (Varidase®) are enzymes excreted by the streptococcal organisms into a culture medium (27). Streptokinase by its catalytic action causes fibrin to be split into polypeptides, thus resulting in dissolution of blood clots and fibrinous exudates This reaction occurs in the presence of serum in an alkaline medium. Streptodornase liquefies deoxyribonucleoprotein and deoxyribonucleaic acid the main constituents in nuclei and causes a reduction in the viscosity of purulent exudates. It does not act upon living cells.

Trypsin Tryptar®) is a crystalline material derived from the pancreas which splits nonviable cells and tissues into polypeptides and amino acids. It acts upon the deoxyribonucleoprotein of the purulent exudate and attacks dead tissue (28).

Steroids

Prednisone (Meticorten®), prednisolone (Meticorteline®), cortisone and ACTH (adrenocorticotropic hormone): These are

tive organisms. This solution has a wide antibacterial spectrum and the sulfamylon is not inhibited by blood exudate.

Aluminum Subacetate: This is used as a 2 per cent solution in distilled water and may be employed for stasis eczema from venous insufficiency, especially if crusted lesions are present. The agent should be stopped if irritation results.

Sulfathiazole Ointment: A 10 per cent ointment in lanolin is bacteriostatic and relatively non-toxic. Patients may become sensitive to this agent so the wound must be inspected at frequent intervals.

Ichthyol Ointment®: This consists of zinc oxide ointment with 3 per cent ichthyol and is valuable as an antipruritic in eczema associated with venous insufficiency. The ointment is applied around the ulcers but not directly on them. A bandage is placed over the ointment.

Gelfoam® Sterile Powder: This is a sterile foam-like powder prepared from specially treated gelation (25). It has tissue stimulating and hemostatic properties and is designed primarily for local application as an aid in promoting growth of granulation tissue and healing of indolent ulcers. It is non-antigenic, non-irritating and has no deleterious effect on the activity of penicillin or streptomycin. It is employed in ulcers due to venous insufficiency, thrombophlebitis, arteriosclerosis, trauma, diabetes and sickle cell anemia. The ulcer is packed with sterile Gelfoam® powder and is covered with a dry gauze. Over this is placed an elastic bandage. Gelfoam® is applied twice weekly until healing ensues. In the presence of secondary infections bed rest with elevation of the affected extremity with wet antibiotic dressings may be necessary first before Gelfoam® is applied.

Tincture of Green Soap: This is useful for removing loose necrotic tissue.

Aureomycin®: This is used as a 3 per cent ointment and is used against pseudomonas aeruginosa and against the pyocyaneous organisms.

Polymyxin-Bacitracin (Polycin®): This is a 1 per cent ointment and is used against pseudomonas aeruginosa and against pyocyaneous organisms.

Centrally Acting Drugs: These are the hydrogenated ergot alkaloids and alcohol.

The DH Ergot Alkaloids (figure 410). These are dilating agents which depress the sympathetic vasomotor system centrally and have an adrenergic blocking effect on the neuroeffector organ in the blood vessels (32). Both of these actions lead to vasodilatation. The drug may be taken in 0 5 mg sublingual tablets three

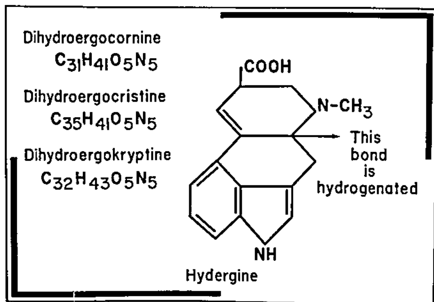


Figure 410 DH alkaloids of ergot act centrally and have vasodilating properties.

or four times daily. It may be given intramuscularly, subcutaneously or intravenously in doses of 0 25 mg. The agent is employed in vasospastic states, especially in the upper etremities when vasoconstriction is present, for example in Raynaud's disease. It has a slight sedative effect which often aids patients with this disease. The sublingual administration in the dosages described does not alter the blood pressure but may slow the pulse rate slightly. When given parenterally in large doses postural hypotension occurs and with the patient in the supine position there is a lowering of blood pressure, slowing of pulse rate, increase in

employed in the treatment of periarteritis nodosa, disseminated lupus erythematosus and scleroderma. Prednisone and prednisolone have little effect on sodium retention and potassium excretion and may be employed in patients on a regular diet. When possible the adrenal steroids are not used for more than 6 weeks at a time because of adrenal supression. In some cases, however, these agents are employed continually for years (29, 30, 31).

Vasoconstrictors

These act by stimulating the sympathetic nervous system or by a direct action on the vessels.

Nicotine: This is a strong vasoconstrictor when taken sublingually and gives a slight but similar effect when inhaled in tobacco smoke. Nicotine is seldom used for its vasoconstrictive effect although it may be of some value in patients with erythermalgia. It acts in part by stimulating sympathetic ganglia as well as directly on the vessel wall itself. Figure 247 shows the effect of smoking one cigarette before and after sympathectomy. The failure of the blood flow to decrease after sympathectomy suggests that the sympathetic ganglia are an important site of action of the drug.

Ergot: This may be given in the form of ergotamine tartrate (Gynergin®) and is a vasoconstrictive agent which has a direct vasoconstrictive action on arterioles. The agent is frequently taken for migraine headache but is of some value in controlling erythermalgia.

Pituitrin: This has been used by nasal insufflation as a peripheral vasoconstrictor for erythermalgia. It acts directly on the vessel wall.

Vasodilators

These act centrally, at sympathetic ganglia, at nerve endings and directly on the vessels. Peripheral blood flow can be increased with vasodilating agents but also the flow can be increased with positive inotropic agents (ones which increase the contractility of the heart muscle) such as Arlidin®.

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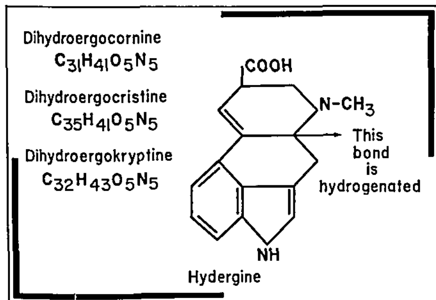


Figure 410 DH alkaloids of ergot act centrally and have vasodilating properties

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skin temperature of the fingers and toes, increased blood flow in fingers and toes with a decrease in spontaneous vasomotor activity of the digits (figure 411), and blocking of the inspiratory sympathetic reflexes (33).

Alcohol: Two ounces orally in the form of whiskey causes a

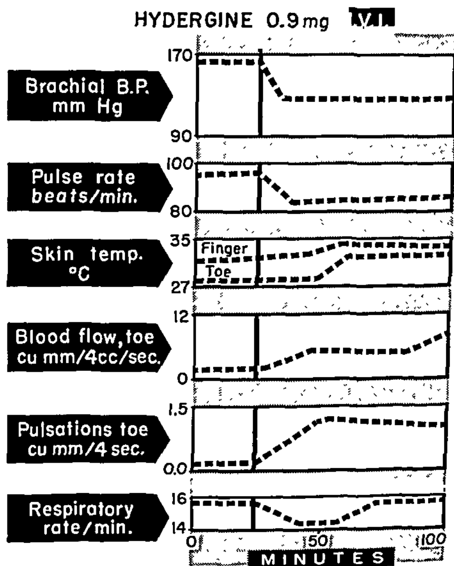


Figure 411. Effect of Hydergine® (CCK 179) 0.9 mg. intravenous in 8 minutes on the circulation.

prompt rise in the pulsations, blood flow and temperature of the digits before as well as after sympathectomy. There is little increase in the circulation of the arms and legs. The blood pressure and pulse rate are essentially unchanged. The results are generally greater than most orally administered vasodilating drugs. The site of action of alcohol is centrally, to decrease sympathetic vasoconstriction and peripherally, acting directly on the blood vessels. Alcohol combined with heating of the body has a stronger peripheral vasodilating effect than does alcohol alone (figure 412). In vascular emergencies, for example with an acute peripheral arterial embolism, two ounces are employed every two or three hours and this amount is reduced as soon as the emergency is over. In patients with diabetes the added caloric intake must be calculated into the diet. The drug is contraindicated in patients with liver disease and in alcoholic patients. Alcohol may be employed after a sympathectomy to produce further vasodilatation because of the direct action of the agent on the blood vessels.

Ganglionic Blocking Agents: These agents produce blocking of autonomic ganglia which results in an increase in circulation to the acral portions of the body. These agents block the sympathetic and parasympathetic systems and are not generally employed in the treatment of ambulatory patients because of hypotension and other undesirable side effects The agents may be employed parenterally or orally for the diagnosis of causalgia. Many ganglionic blocking agents are available but because of their limited usefulness in patients with peripheral vascular disease only chlorisondamine (Ecolid®) and mecamylamine (Inversine®) will be mentioned here.

Chlorisondamine Chloride (Ecolid®) (34): This is a long acting ganglionic blocking agent. The average dose is 75 to 100 mg twice daily at ten to twelve hour intervals. This level is achieved after a trial with smaller doses. Side effects are postural hypotension, blurring of vision and constipation. Relief of causalgic pain may occur after the oral administration of this agent. A rapid effect is obtained when 10 mg of the drug is given intravenously.

Mecamylamine Hydrochloride (Inversine®): This is a ganglionic blocking agent which is effective as a vasodilator in small doses. The usual dose is 10 mg orally three times a day. This dose is

arrived at after smaller doses have been tried first. Intravenously 5 mg is effective.

Adrenergic Blocking Agents: These are tolazoline (Priscoline®), phenoxybenzamine (Dibenzyline®), phentolamine (Regitine®) and azapetine (Ilidar®). These are preferable to ganglionic blocking agents as they inhibit sympathetic nerve activity without interfering with the parasympathetic nervous system.

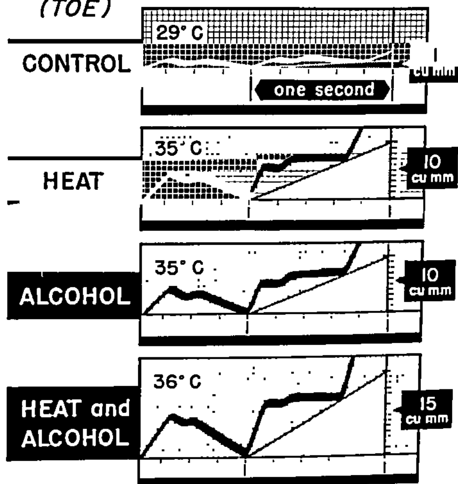


Figure 412. Body heating and alcohol are more effective vasodilators than either alone.

Tolazoline Hydrochloride (Priscoline®) (figure 413) (35): This agent has adrenergic blocking and sympatholytic properties (figure 414). The adrenergic blocking effect occurs at a lower dosage than does the sympathetic blocking effect. The agent increases skin temperatures, peripheral blood flow and pulsations of the digits in normal individuals and in patients with peripheral vascular disease when functional vasoconstriction is present. The

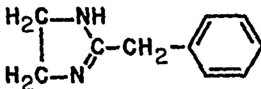


Figure 413. Priscoline® is a relatively effective oral peripheral vasodilator

agent is a more effective dilator of the lower extremities than of the upper (figure 41). The induced digital vasoconstrictor reflexes are blocked. The usual oral dose is 25 mg three to four times daily. The side effects are tingling of the scalp, a crawling sensation of the skin, tachycardia and nervousness. It may be employed intramuscularly in doses of 20 to 30 mg three or four times a day.

Phenoxybenzamine Hydrochloride (Dibenzyline®) (figure 415) (36): This is an adrenergic blocking agent which acts at the sympathetic nerve endings and does not have an effect on the parasympathetic system It produces a chemical sympathectomy. The agent increases blood flow in the normal extremity and in patients with organic arterial disease when functional vasocon-

striction is present. The peripheral blood flow and skin temperatures are increased. Usually the drug is given by mouth in doses of 10 mg three times a day, however it may be given in 5 mg doses parenterally. The agent is indicated in vasospastic states, frost-

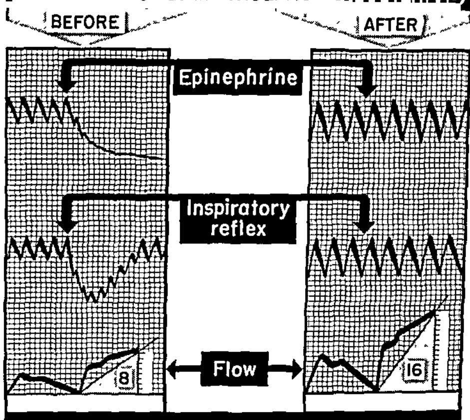


Figure 414. Priscoline has adrenolytic, sympatholytic and vasodilating properties.

bite, causalgia and in patients with organic arterial disease. This agent is indicated after interruption of postganglionic sympathetic nerve fibers when a *sensitivity* to epinephrine has occurred (*figure* 36).

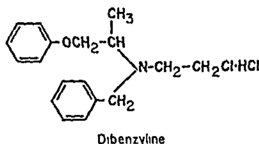


Figure 415. Dibenzyline® is a fairly well tolerated adrenergic blocking agent which may be employed as a peripheral vasodilator.

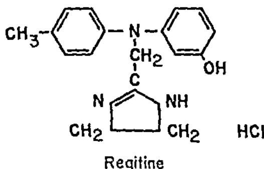


Figure 416 Regitine® is an adrenergic blocking agent which is more useful for the diagnosis of chromaffin tumors than as a peripheral vasodilator.

Phentolamine Hydrochloride (Regitine®) (figure 416) (37): This is an adrenergic blocking agent which has been employed widely for the diagnosis of chromaffin tumors. The agent blocks the sympathetic nervous system at the nerve endings and effectively reverses the normal hypertensive action of injected epi-

nephrine and suppresses the pressor response of nor-epinephrine (figure 417). The blood flow through the extremities is increased in normal subjects and in certain patients with peripheral vascular disease. A sympatholytic effect is shown by the blocking of the induced vasoconstrictive reflexes. Little if any direct vasodilating effect on the vessel wall is exerted In peripheral vascular disease the agent is usually administered orally in doses of 30 mg three or four times daily, if tolerated. The agent is a poor vasodilator com-

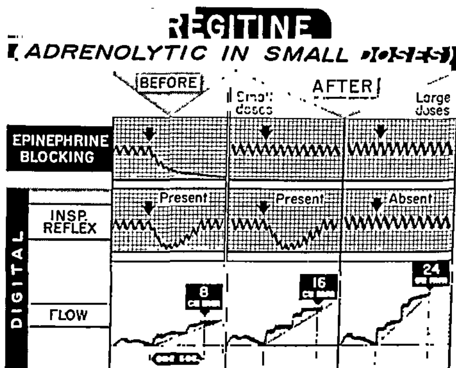


Figure 417 Regitine® is adrenolytic but is not sympatholytic in small doses. In large doses it is both adrenolytic and sympatholytic.

pared with a posterior tibial nerve block. When employed parenterally for testing for chromaffin tumors, 5 mg is given intravenously or intramuscularly.

Azapetine Phosphate (Ilidar®) (figure 418) (38): This is a short acting adrenergic blocking agent with some direct vasodilating action on the vessel wall. The drug increases the peripheral cir-

culation by inhibiting vasoconstriction and in large doses causes a fall in blood pressure. In certain cases with functional vasoconstriction it provides relief from aching, numbness, tingling and blanching of the extremities. An oral dose of 75 to 125 mg three times daily is employed. Smaller doses are given parenterally (1 mg per kilogram of body weight in 250 cc of normal saline solution) by slow intravenous drip. Following the parenteral administration hypotensive reactions may occur which can be

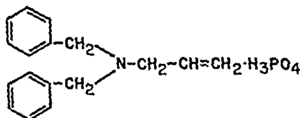


Figure 418. Ilidar® is a short acting adrenergic blocking agent which has some direct vasodilating action on blood vessel walls

reversed by elevating the legs or by employing a vasoconstrictor such as phenylephrine (Neosynephrine®) 10 0 mg intramuscularly or a smaller dose intravenously. Mild gastrointestinal distress and nasal stuffiness have been reported.

Direct Acting Vasodilators: These are Roniacol®, nitroglycerin and alcohol.

Beta pyridil carbinol (Roniacol®) (figure 419). This is the alcohol corresponding to nicotinic acid and has a direct vasodilating action on the arteries especially of the upper extremities (figure 420) The oral dose of the prompt acting drug is 100 mg three or four times a day. Larger doses can be given when the long acting tablets are employed. The dose should be pushed to tolerance for maximal effect. The agent produces slight vasodilatation

after a lumbar sympathectomy and is of value after this operation. The side effects are a tingly sensation, warmth and blushing of the face, neck, shoulders and arms which occur after an adequate dosage. The drug is safe and is of value only if large enough doses are employed (39).

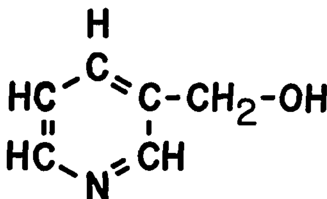


Figure 419 Roniacol® is an alcohol which corresponds to nicotinic acid which has a direct vasodilating action on the arteries

Nitroglycerin: This is employed at times as a peripheral dilator for restless legs when due to ischemia of tissues.

Alcohol: This has a peripheral effect due to a direct action on the vessel as shown by vasodilatation which occurs after a sympathectomy. This drug acts centrally also.

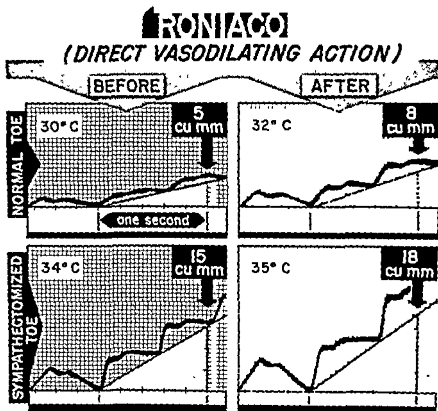


Figure 420. The vasodilating properties of Roniacol® may be demonstrated when large doses are employed. Vasodilatation may be produced in a sympathectomized limb which indicates that the drug acts directly on the blood vessel wall.

POSITIVE INOTROPIC AGENT

An effective drug acting directly on the heart muscle and on blood flow through skeletal muscle is norsuprifen (Arlidin®).

Nofsuprifen (Arlidin®) (figure 421): This is phenyl-2-butyl-norsuprifen. This is an agent related to epinephrine which produces an increase in blood flow to the skeletal muscles and increases the cardiac output and coronary circulation along with a slight decrease in mean arterial pressure (40). The oral dose is 6 mg three or four times a day and may be given by subcutaneous or intramuscular injection. The agent is indicated in patients with

after a lumbar sympathectomy and is of value after this operation. The side effects are a tingly sensation, warmth and blushing of the face, neck, shoulders and arms which occur after an adequate dosage. The drug is safe and is of value only if large enough doses are employed (39).

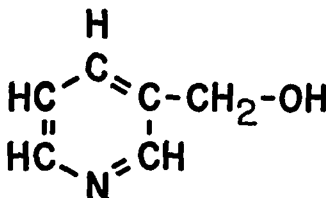


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Vaccines and Antitoxins

Vaccines: Typhoid vaccine has been employed for the production of vasodilatation. This type of therapy produces vasoconstriction alternating with vasodilatation. Therapy with this agent has been employed for Buerger's disease.

Antitoxins: Gas gangrene antitoxin should be given to patients with ulcers or gangrene with blebs as a prophylaxis against intoxication from the gas gangrene bacillus. The dose is 3000 units intramuscularly.

Vitamins

Vitamin B_{12} is of value in patients with diabetic neuritis. Occasionally patients with ischemic neuritis may show some improvement. One hundred micrograms injected intramuscularly daily is employed for about ten days as a therapeutic test. It is felt by some that vitamin B complex should be injected also to produce balanced vitamin therapy. If this therapy is successful, the shots may be given three times weekly supported by daily oral doses of vitamin B_{12} in doses of 120 micrograms. Oral B_{12} (Orexin®) may be effective.

Drugs Which Do Not Augment Peripheral Flow: The drugs which do not give plethysmographic evidence of augmented peripheral circulation are calcium, theobromine, theophylline, sodium thiosulfate, iodides, sodium tetrathionate, magnesium sulfate, cobra venom, tissue extract, alpha tocopherol, ether, histadine, vitamin E and tetrathione

PHYSICAL THERAPEUTIC PROCEDURES

The useful procedures are: 1) heating of the body; 2) oscillating bed, 3) leg cradles with heat; 4) leg cradles without heat; 5) foot supports, and 6) postural exercises.

Heating of the body: The application of electric pads, hot water bottles or other heat sources to the trunk of the body result in vasodilatation of the normal extremity. The cause of the vasodilatation is the presence of warm blood in the brain which produces a decrease in sympathetic vasoconstrictor tone. This mechanism is illustrated by an experiment in which an arterial occlud-

intermittent claudication, diabetic vascular disease, thromboangiitis obliterans, night cramps and other abnormalities. The increased blood flow which occurs in the skeletal muscles of the limbs is of interest because few vasodilators increase the circulation in this area. Nervousness and palpitation may occur; however, this recedes or disappears upon continued administration of the drug. It should be used cautiously in patients with hyperthyroidism, paroxysmal tachycardia, angina pectoris or after a coronary thrombosis.

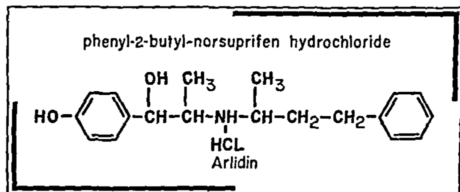
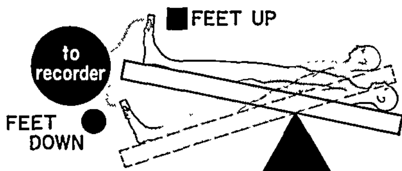


Figure 421. Arlidin® is a vasodilator which is related to epinephrine which produces an increase in blood flow to skeletal muscle.

Combined Use of Drugs to Increase Blood Flow: The most satisfactory vasodilating technique is to employ a combination of drugs, each of which has a different mechanism of action For example, Priscoline®, Roniacol® and Hydergine® may be combined. Priscoline® is an adrenergic blocker, Roniacol® has a direct action on vessels and Hydergine® has a central dilating effect. Also Arlidin®, Dibenzyline®, and alcohol may be used. These act on the heart, sympathetic nerve endings and vessels, respectively. When combinations of agents are used along with gentle body warming a satisfactory amount of vasodilatation often can be produced; however, a sympathectomy generally produces a greater amount of vasodilatation than is produced by these means. After a sympathectomy those agents acting directly on the vessel, for example Roniacol® and alcohol, should be used

OSCILLATING BED

AND TOE VOLUMES — cu mm



A BEFORE SYMPATHECTOMY



B AFTER SYMPATHECTOMY



Figure 422. The oscillating bed is employed to increase the circulation to the limb and at the same time prevent venous congestion The technique is more effective after vasodilatation, for example after a sympathectomy. In (A) the volume changes of the toe which occurred with the oscillation of the bed as measured plethysmographically were relatively slight before the sympathectomy. In (B) after the sympathectomy the volume changes were considerably greater.

ing tourniquet is placed on the arm and the arm placed in warm water, and the skin temperature of the toe measured. As long as the tourniquet stays in place, preventing the warm blood from leaving the arm, the temperature of the toe does not increase. When the tourniquet is removed the skin temperature increases. The vasodilatation is due to the release of the warm blood from the arm and to its presence in the brain. In patients with localized arterial disease, for example of the digital arteries, mild body heating often increases the circulation, however intensive body heating results in a decreased flow to the diseased area. In critical cases it is desirable to determine the exact amount of heat which is beneficial or harmful. This can be done by performing the venous congestion test at intervals during body heating.

Oscillating Bed (figure 422): The Sanders oscillating bed is of slight value in the treatment of peripheral arterial disease. It is indicated in patients with ulceration of the skin of the legs or feet and its use facilitates healing (41, 42). The bed is employed most effectively when vasodilators are administered simultaneously. Figure 422 shows the volume changes of the toes which occur during the oscillation of the bed recorded plethysmographically before and after a lumbar sympathectomy. The movement of the bed serves as a peripheral pump which facilitates the exchange of intra and extravascular fluids. The bed should be adjusted for the minimum foot-up and maximum foot-down position and it should be bent at the knee so the patient does not slide toward the foot of the bed when the feet descend. With this adjustment the feet are below heart level for a long period of time and are at, or very slightly above heart level for a short time. Thus gravity pulls blood into the feet through the arterial system during the greater period of the cycle during the foot down position and the feet are in the elevated position only long enough to produce venous dumping but not long enough to produce significant ischemia. The rocking bed prevents edema of the tissues which would occur if the foot of the bed remained in a fixed foot-down position for long periods of time.

Leg Cradle Without Heat (figure 423): Cradles which support the blanket at the foot of the bed are of value for protecting the feet against abrasion. The feet should be wrapped in cotton wad-

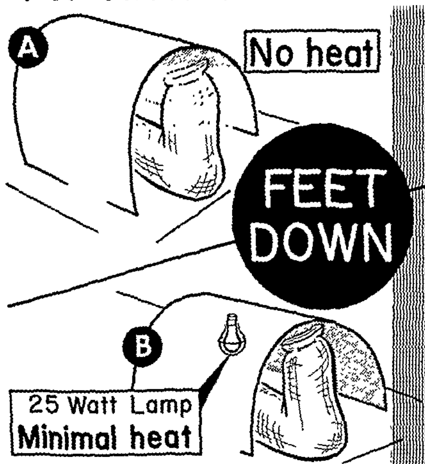


Figure 423 In treating arterial disease the leg is covered with stockinette and a cradle is placed over the foot to prevent damage from the weight of the bed clothes. In (A) no heat is employed. In (B) a small lamp (25 watts) is employed to maintain minimal heat The foot-down position is desirable.

ding or stockinette and a 25 watt lamp inside the cradle may be used to prevent heat loss.

Leg Cradle With Heat (figure 424): This is important in the treatment of venous diseases. The cradle should be high enough so that the legs may be elevated and surrounded by hot wet packs yet still be covered by the cradle. A 25 watt lamp properly protected usually provides adequate heat for arterial disease, however, larger lamps (75 watt) may be used for venous disease when wet packs are to be kept warm.

Foot Supports (figure 425): Supports for elevating the feet prevent foot drop and are important if patients are to be kept in bed for long periods of time.

Postural Exercises: The classical exercises of Buerger consist of the following: The legs are elevated on 3 pillows until they are ischemic as shown by paleness or ischemic pain. The patient then sits on the bed with the legs dependent until reactive hyperemia develops and recedes (until they become red and the redness subsides). He then rests in a horizontal position for a few minutes after which he repeats these positions. These exercises are of value in that the interchange of serum and tissue fluids is accelerated by the changing effect of gravity on the blood and tissue fluids in the legs and feet, however, the foot-up position is undesirable because this produces ischemia. It is probable that the ischemia produced is greater than the augmentation of the flow which results from reactive hyperemia.

Modified Postural Exercise for Patients With Severe Arterial Disease (figure 401): These are as follows: The legs are horizontal for ten minutes and then down for ten minutes. These positions are repeated for one hour three or four times a day. These exercises are of value as a means of relieving pain, improving the circulation, and preventing congestion of the tissues. At no time is the foot-up position assumed because with severe arterial disease ischemia is present even in the horizontal position.

SURGICAL TREATMENT

This consists of: 1) sympathectomy; 2) arterial grafts; 3) vein grafts; 4) plastic prostheses; 5) embolectomy; 6) thromboen-

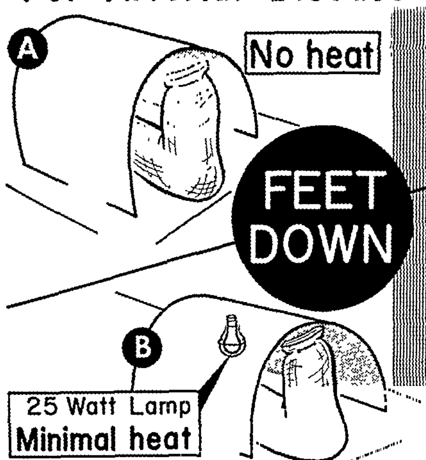


Figure 423 In treating arterial disease the leg is covered with stockinette and a cradle is placed over the foot to prevent damage from the weight of the bed clothes In (A) no heat is employed. In (B) a small lamp (25 watts) is employed to maintain minimal heat. The foot-down position is desirable.

darterectomy; 7) arterectomy; 8) arterial shunts; 9) amputation, 10) tenotomy, 11) nerve crush, and intra-arterial therapy.

SYMPATHECTOMY

This is employed to increase the circulation to the hands and arms and to the toes and feet and distal thirds of the legs (43).

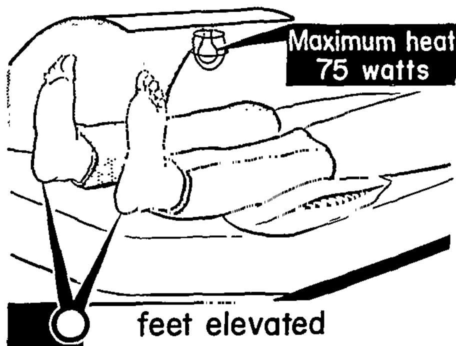


Figure 424. For venous disease the legs are elevated and more intense heat is applied (75 watts).

This procedure is used when disease of small vessels is present (in diabetes) or when it is impractical to restore the patency of large arteries by thromboendarterectomy or graft. Careful clinical and laboratory studies of the circulation should be made before surgery

to estimate the possible benefits of sympathectomy. The sympathectomy should be carried out so that a decrease in peripheral resistance occurs only distal to the obstruction as this results in an increase in blood flow in the area where blood is needed. If dila-

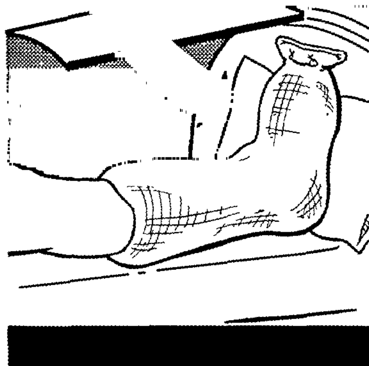


Figure 425. A foot support in the form of a pillow is employed to prevent foot-drop

tation of vessels occurs proximal to the obstruction the distal portion of the limb may be deprived of blood or flow will increase only slightly. The sympathectomy is a relatively simple and safe operation which can be performed quickly and without shock.

Clinical Indications: The major indication is the demonstration of a large amount of sympathetic vasoconstrictor activity in the diseased limb. A history of cold feet during the day but warming of the feet at night is helpful as it suggests that vasomotor activity is present. This information does not determine if the vasomotion occurred because of sympathetic nerve activity or because of humoral or chemical influences. The presence and degree of functional vasoconstriction can be detected by noting an increase in skin temperature of the feet after a posterior tibial nerve block which can be performed as an office procedure. Here the vasodilatation results from removal of sympathetic nerves which is similar to that produced by surgery. Sympathectomy is indicated especially when atrophy of the skin, loss of hair or other skin changes are present and when slowly progressive skin deterioration is taking place. Excessive sweating also is an indication for sympathectomy.

Laboratory Indications: A sympathectomy is indicated in those diseases in which the examination suggests that vasodilatation will result from removal of sympathetic nerves. The probable outcome of a lumbar sympathectomy (figure 426) may be estimated by determining after a vasodilating procedure the: 1) rate of blood flow through a toe; 2) potential blood flow; 3) magnitude of the inspiratory reflex; 4) magnitude of the slow waves of the plethysmogram, 5) height of pulse waves of the toes, and 6) skin temperatures of the toes (44).

Rate of Blood Flow Through a Toe: When the rate of blood flow through a toe using an ankle occluding cuff after a posterior tibial block is from 10 to 18 cu mm per second the results of sympathectomy generally will be good (mild organic arterial disease). When it is 1 to 3 cu mm per second the results usually will be poor (advanced arterial disease).

Potential Blood Flow (figure 178): This is a measure of the increase in flow which can be produced by the block over that which exists naturally with the patient resting in a comfortable environment, and identifies the amount of sympathetic vasoconstriction which was present at the time of the block. A potential blood flow up to 100 per cent indicates weak sympathetic vasoconstriction and suggests a poor outcome after surgery whereas a

PREDICTING OUTCOME OF SYMPATHECTOMY

	GOOD	POOR
Toe flow cu mm/sec. Ankle cuff after block	10-18	1-3
Potential flow after block % increase	500 to 1800	0 to 100
Insp. reflex cu mm After heat and alcohol	30-50	0-10
Slow waves cu mm with indirect body heating	30-50 Class Z	0-10 Class X
Pulse height cu mm Toes after block	4-9 Classes II or III	0-1 Class I
Skin temp. °C toe after block Rm. temp. 23 °C	33-36	23-30

Figure 426 Vascular studies assist in predicting the probable outcome of a sympathectomy.

potential blood flow of from 500 to 1800 per cent indicates strong sympathetic vasoconstriction and suggests a good response from surgery.

Inspiratory Reflex (figure 163): The test is carried out after first producing vasodilatation by body heating and two ounces of whiskey. A large inspiratory reflex occurs when organic disease is minimal and a small reflex occurs when organic disease is maximal. The results of sympathectomy usually are excellent when a large reflex (30 to 50 cu mm) is present. When a small reflex occurs (0 to 10 cu mm) the results often are poor. It is important to obtain maximum vasodilatation with alcohol and heat before the reflex is elicited.

Slow Waves (figure 155): The magnitude of these waves is related to the outcome of a sympathectomy. When during the course of body heating the waves are large (30 to 50 cu mm, Class Z) the outcome of surgery often is excellent and when they are small (0 to 10 cu mm, Class X) the outcome often is poor.

Pulse Waves of the Toe: A good surgical result occurs usually if the pulse heights after a tibial block are large (4 to 9 cu mm, Classes II and III) and poor results occur if the heights are small (0 to 1 cu mm, Class I).

Skin Temperatures (figure 249): These are of only moderate value in predicting the outcome of sympathectomy. The skin temperature must be considered in relation to the room temperature. With a room temperature of 23 degrees C a good effect from sympathectomy usually occurs when after a block the skin temperature of the toe is from 33 to 36 degrees. A poor result occurs when the temperature increases to less than 31 degrees.

Contraindications: Severe cardiac or cerebral disease are contraindications as these states increase the operative mortality. Sympathectomy is contraindicated in advanced obliterative arterial disease especially when hemometakinesia is demonstrated preoperatively by a posterior tibial nerve block (fall in skin temperature and blood flow to the toes after this procedure) (45).

Ganglia Removed: The portions of the sympathetic system removed differ greatly with different surgical techniques. Sympathectomy of the lower extremities (figure 14) usually involves removing the second and third lumbar ganglia which produces a

preganglionic sympathectomy as far as the legs are concerned and the foot is usually sympathectomized completely. Occasionally the sympathectomy is incomplete which occurs when some of the sympathetic fibers from the spinal cord do not enter the sympathetic ganglia as shown in figure 3. The thoracic sympathectomy is carried out by removing the second or second and third thoracic ganglia (46) (figures 10, 11, 12). Most of the preganglionic fibers to the arm are interrupted by removing the second thoracic ganglion as shown by drying of the skin of the face and arm on the ipsilateral side. A Horner's syndrome is produced when the first thoracic ganglion is removed but does not occur if the second thoracic ganglion is removed.

Circulatory Changes After Sympathectomy (figure 427): The various effects of sympathectomy are: distention of the veins; increased blood flow, pulsations and skin temperatures of the digits; decrease in sweating and interference with vasoconstrictive reactions to inspiration, cold, pain and anticipation. Heat loss through evaporation is prevented as the sympathectomized limb is dry. The normal vasoconstrictor response of the blood vessels on standing is inhibited. The blood flow in the limb does not fluctuate from moment to moment as shown by the absence of slow waves of the plethysmogram. There is an increased rate of warming of the tissues once they have been cooled and a cold environment produces less cooling of the part after surgery than before. Hair growth and growth of nails may occur more rapidly than before surgery and in about half of the patients a slight increase in walking ability occurs.

Side Effects: Postoperative neuritis is a disturbing complication and occurs in from 10 to 20 per cent of patients and may be the result of trauma or irritation of nerve trunks. The pain is often in the cutaneous distribution of the femoral cutaneous nerve (figure 16). The pain lasts from one to three months and usually disappears completely even though untreated The neuritis usually appears ten to fourteen days after surgery (47). If all four limbs are sympathectomized impairment of the temperature regulating mechanism may occur because of the widespread hypohydrosis. Gangrene precipitated by sympathectomy is a rare phenomenon and probably can be anticipated preoperatively by

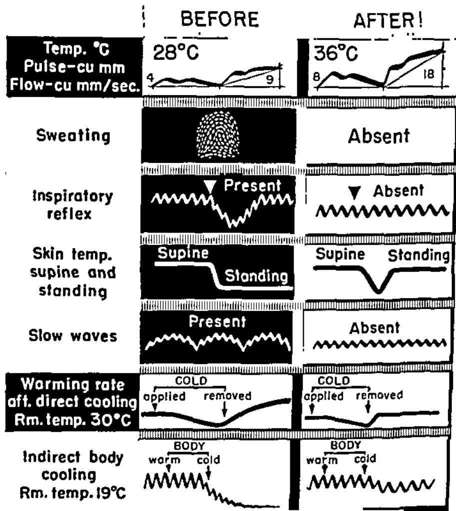


Figure 427. The beneficial effects of a lumbar sympathectomy may be demonstrated by vascular studies.

noting a decrease in circulation of the digits following a posterior tibial nerve block (48). If both first lumbar paravertebral sympathetic ganglia are removed ejaculation is difficult. The dry skin of the sympathectomized limb may require the daily use of hydrated lanolin.

Arterial Grafts

These have been employed successfully: 1) to repair weakened or dilated vessels; 2) to restore the patency to previously obstructed arteries, and 3) as temporary or permanent shunts to bypass obstructions in an artery. Arterial grafts have been transplanted successfully into the arterial and venous systems.

Indications for a Graft: Grafts are employed for end to end anastomosis in the following situations: 1) arterial aneurysms of the thoracic or abdominal aorta, iliac, femoral, popliteal and other large and medium size arteries; 2) obstructions of large or medium size arteries, for example obstruction of the abdominal aorta which produces the Leriche syndrome, 3) trauma to an artery; 4) coarctation of the aorta when the coarctation is too long for direct end to end anastomosis, 5) tetralogy of Fallot when it is necessary to lengthen the subclavian artery to complete the anastomosis to the pulmonary artery, 6) when widening of the pulmonary artery is desirable for treatment of congenital heart disease, 7) for the repair of arteriovenous fistulas for restoration of the artery, 8) for the removal of tumors of arteries when resection and replacement of vessels is necessary when the tumor involves the vessel wall; 9) for repair of an obstructed superior vena cava, and 10) to produce a portal caval shunt Some of these indications are shown in figure 428. When employed for shunts around obstructions or aneurysms they may be temporary or permanent (figure 429) (49, 50, 51).

Vein Grafts

These have been employed for transplantation into the arterial or venous system. Often the femoral vein is transplanted into medium size arteries such as the popliteal. Vein grafts have a tendency to dilate or calcify and in general arterial homografts are preferred.

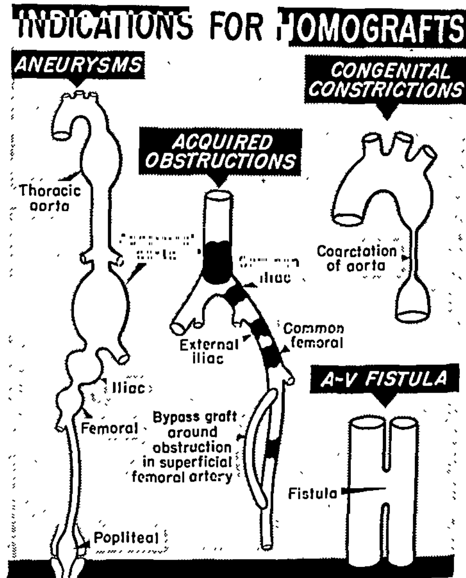


Fig. 428. Common indications for an arterial homograft.

Plastic Prostheses

These usually are flexible but may in certain cases be rigid. Flexible grafts are preferred for most purposes because they expand and contract with each cardiac pulsation. The substances employed are Vinyon N, Nylon, Orlon, Dacron and Teflon

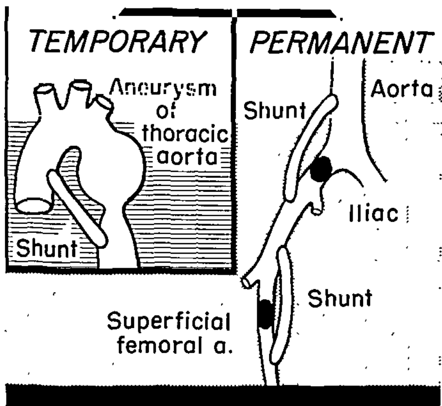


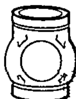
Figure 429 Indications for an arterial shunt.

(figure 430). The flexible, non-corrugated tubes are prepared by stitching the material using thread of the same material as the fabric. Straight or Y-shaped tubes may be fabricated. Before use the prostheses are immersed in 10 per cent aqueous solution of a detergent such as the Alconox wetting agent* for twelve hours to eliminate oil and foreign matter which may accumulate during sewing. The cloth is then rinsed in distilled water or saline before use. For sterilization Orlon and Dacron may be autoclaved while Nylon and Vinyon N must be boiled for fifteen minutes. The

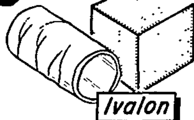
* Alconox, Inc, Jersey City, New Jersey.

ARTERIAL PROTHESES

A RIGID



B SEMI-RIGID



C FLEXIBLE

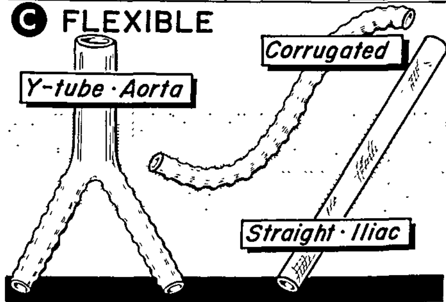


Figure 430 Arterial prostheses may be employed for end to end arterial anastomosis or for by-passing obstructions

prosthesis should fit the arterial defect precisely to prevent buckling of the graft which may result in thrombosis. A plastic flexible corrugated graft has been described by Tapp and Edwards which turns corners without buckling * Teflon sponge can be molded into an artery but arterial homografts are preferred usually (52).

* Union Carbide Company, New York, A. Lamport and Bros, New York; C. P. Banning Corp, Central Valley, New York.

Embolectomy

This is indicated usually when the embolus has been present for only a few hours because after this time proximal or distal thrombosis may occur in the artery (figure 347) (53, 54). If the collateral circulation is poor or if the flow is poor distal to the obstruction thrombosis occurs readily. It is common for thrombosis to occur proximal to the embolus up to the first major branch of the obstructed artery. As soon as the embolus is recognized clinically heparin should be given intravenously at 4 hour intervals up to the time of surgery. Embolectomy is attempted usually when the embolus involves the aorta, iliac, femoral or popliteal artery. After surgery anticoagulants are given in the form of heparin and dicoumarol. After a few days the heparin is stopped and dicoumarol may be continued for about 3 weeks. When the embolus involves small arteries such as the distal portions of the anterior or posterior tibial artery embolectomy may not be practical because of the small size of the vessels. Here a lumbar sympathectomy may be of value. Before this is done a posterior tibial nerve block may be performed to determine if a sympathectomy would be of value. If the block produces adequate circulation to the toes it is probable that a lumbar sympathectomy would be helpful.

Thromboendarterectomy

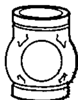
This was performed first by Dos Santos in 1946 when he removed from an artery an obstruction which consisted of intima, media, clotted blood and calcium. Since, the procedure has been employed widely for restoring the lumen of large arteries such as the iliac or femoral arteries (figure 431).

Indications: The procedure is employed when large arteries are obstructed by short lesions when the artery distal to the obstruction is patent.

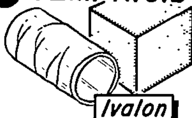
Contraindications: The procedure generally is contraindicated when: diffuse arterial disease is present with involvement of large, medium and small vessels, when obvious gangrene is present, in the presence of spreading infection and when the disease extends so far into the media of the vessel wall that removal of the occlu-

ARTERIAL PROTHESES

A RIGID



B SEMI-RIGID



C FLEXIBLE

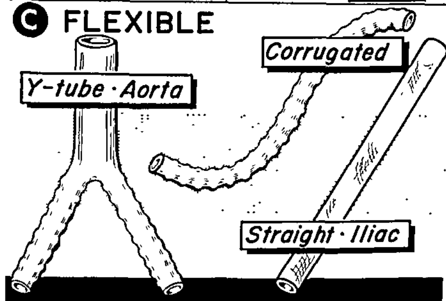


Figure 430. Arterial prostheses may be employed for end to end arterial anastomosis or for by-passing obstructions.

prosthesis should fit the arterial defect precisely to prevent buckling of the graft which may result in thrombosis. A plastic flexible corrugated graft has been described by Tapp and Edwards which turns corners without buckling.* Teflon sponge can be molded into an artery but arterial homografts are preferred usually (52).

* Union Carbide Company, New York, A. Lamport and Bros, New York, C. P. Banning Corp, Central Valley, New York.

Technique: A longitudinal incision is made over the obstructing lesion. A point of cleavage is found where one can separate the obstructing material from the vessel wall. After removal of the obstruction the vessel is reconstructed by carefully suturing the external coats of the artery. Clotting is prevented by the use of anticoagulants. Usually heparin, 10 mg is injected periodically during the course of the operation, however the total amount of heparin used during an operation does not exceed 40 mg. The inner lining soon endothelializes but prior to the endothelialization there is a layer of leukocytes which lines the vessels and carries on the function of an endothelium until such time as endothelialization occurs.

Arterectomy

The removal of an arterial segment with its obstructing contents has been advocated by Leriche on the theory that the obstructed artery is a source of irritation which results in vasoconstriction (55). An arterectomy is not generally employed when restoration of the lumen of the artery by a graft or thromboendarterectomy is possible.

Arterial Shunts

These may be temporary or permanent and may consist of prosthetic material, for example plastic tubing or arterial homografts or heterografts. Temporary grafts have been employed to prevent ischemia of the spinal cord when prolonged clamping of the aorta is necessary (repair of aneurysms of the thoracic aorta) Permanent bypass grafts are used successfully for the bypass of lesions in the aorta, iliac or femoral arteries (51) (figure 429).

Amputation

An attempt should be made to amputate at the lowest possible site which is consistent with the possibility of good healing One important factor which influences the healing process is the blood supply to the part The circulation should be judged clinically by palpating the pulses and examining for reactive hyperemia and noting the venous filling time after elevation and dependency of the limb. In addition to the clinical tests objective measure-

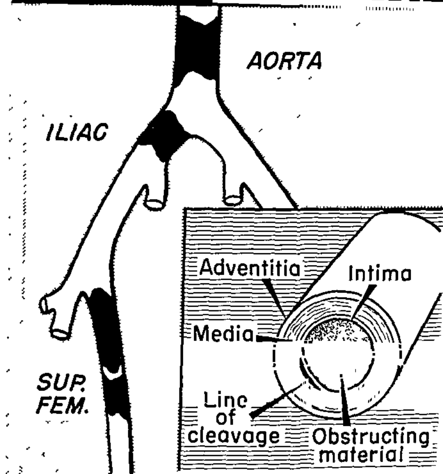


Figure 431. Sites suitable for thromboendarterectomy.

sion will not leave a vessel wall adequate to give support for the blood.

Complications: These are dilatation of the artery *with aneurysmal formation, rupture, hemorrhage and thrombosis.* Thrombosis occurs especially when obstructing lesions are present distal to the site of thromboendarterectomy because the blood flow through the operated region is slow.

procedure when the resection of a single digit would be satisfactory.

Tarsal Amputation (Syme and Lisfranc): Tarsal amputation may be carried out if clinical and segmental plethysmographic studies indicate that arterial disease is present at the metatarsal area but absent *in the tarsal region.*

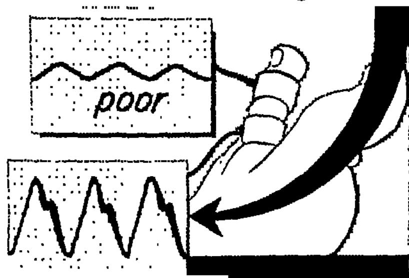


Figure 432 A digital amputation may be performed when the tip of the digit pulsates poorly but the base of the digit pulsates normally

Below the Knee Amputation (figure 434): A below the knee amputation may be performed if the plethysmographic study indicates a good pulsation and systolic blood pressure with good pulsation indexes below the knee and at the calf, when infection is absent and when an incision at the time of surgery indicates a good blood supply at the proposed amputation level. A sympathectomy may be performed first to increase the circulation through the skin but is of questionable value. Amputation below the knee usually is not advocated if patients are severely debili-

ments with the plethysmograph are of value. Clinical and laboratory examinations assist in determining the necessity and site for amputation. From the laboratory point of view an amputation often will be necessary when after a posterior tibial nerve block: 1) the skin temperature of a digit is below 29 degrees when the room temperature is 24 degrees, 2) the venous congestion test (extremity cuff) is less than 1.5 cu mm per second; 3) there is no demonstrable pulsation of the digit; 4) the ankle pulse is below 0.01 ml; 5) the ankle/wrist pulse ratio is below 0.04; 6) the systolic blood pressure at the ankle is less than 30 mm Hg, and 7) the ankle/wrist blood pressure ratio is less than 0.2. When all or most of these findings are present it is unlikely that the tissues will survive for a long period of time.

Amputation of Part of Digit: A portion of necrotic toe may be permitted to demarcate especially if gangrene is dry. The dead portion may be removed with a rongour if infection is absent. Healing occurs slowly by granulation. Often wedge resection of the necrotic tissue and bone is performed without suturing. The area is left open and sterile soaks and local antibiotics are employed until healing of the open wound occurs. Amputation of part of a digit is carried out when it can be demonstrated that a distal portion of a digit is ischemic while good circulation is present proximally. This can be demonstrated with the aid of the segmental ring plethysmograph. If the ring is over the ischemic area small pulsations are present (figure 432) but if it is placed over the proximal area of the digit with good circulation normal pulsations are present.

Disarticulation of the Toe (figure 433): This is performed when an entire toe shows poor circulation when the circulation at the foot is good.

Transmetatarsal Amputation (McKittrick) (figure 433): The purpose of the procedure is to remove one or two ischemic toes and to prevent gangrene from developing in the other toes (56). The surgery is performed when there is no spreading infection and when the dorsalis pedis and posterior tibial arteries are patent. Plethysmographic studies are of aid in determining the patency of these arteries distal to the sites where they are accessable for palpation. Often healthy toes are lost unnecessarily with this

patient has severe debility, for example cardiacs who are not expected to walk postoperatively (58).

Refrigeration: This is employed prior to amputation and may be used to decrease the metabolism of the part, diminish the absorption of toxic products into the system and to decrease cellular

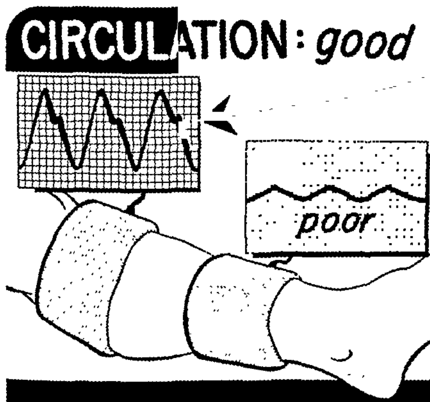


Figure 434. A below the knee amputation may be indicated if the ankle pulsates poorly but the calf pulsates normally

metabolism and retard infection. The part may be cooled with ice and a tourniquet applied to the leg above the ice pack. Refrigeration is indicated where there is rapidly spreading infection, with advanced gangrene, in debilitated patients who cannot stand anesthesia and in uncontrolled diabetic patients with infection. The leg is wrapped in thin rubber sheeting which is placed in

tated or have advanced cardiac, renal or cerebral disease or if the patient would not be able to stand a second operation at a higher site if one would be necessary (57).

Above the Knee Amputation (figure 435): This is performed when there is evidence of popliteal arterial disease as shown by

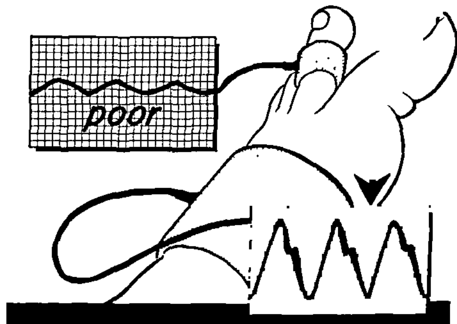


Figure 433. Transmetatarsal amputation may be carried out if a toe pulsates poorly but the foot pulsates normally

absent popliteal pulsations by palpation and when the plethysmographic examination shows a sharp decrease in systolic blood pressure and amplitude of pulsation below the knee as compared *with above the knee. An amputation at this site* is carried out often when: there is uncontrolled infection in the foot, there is gangrene of the lower leg, when an incision at the time of surgery *below the knee shows avascularity* of the tissues and when the

anesthetic which is a source of considerable concern to most patients. The nerves which may be crushed easily are the saphenous, superficial peroneal, sural, deep peroneal and posterior tibial. *Analgesia, anesthesia and motor paralysis remain lost for from* three to six months and sensitivity to epinephrine may develop because the post ganglionic sympathetic nerves are interrupted. This procedure is in general not satisfactory (58).

Intra-arterial Therapy

Such agents as Priscoline®, Hydergine®, histamine, acetylcholine, nicotinic acid, papaverine and procaine may be injected intra-arterially (61, 62). This method of administration is indicated only rarely for acute vascular disease such as an acute arterial *embolism. It is not indicated for the treatment of chronic vascular disease.* A definite risk is involved when an intra-arterial needle is inserted repeatedly into a diseased artery because of direct trauma and vasospasm. This procedure is not employed widely.

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chipped ice. Appropriate sedatives are administerd. The ice is removed when the patient is in the operating room (59).

Tenotomy of the Tendo Achilles

This procedure is employed for intermittent claudication of the calf muscles. The ischemic pain is diminished as the metabolic

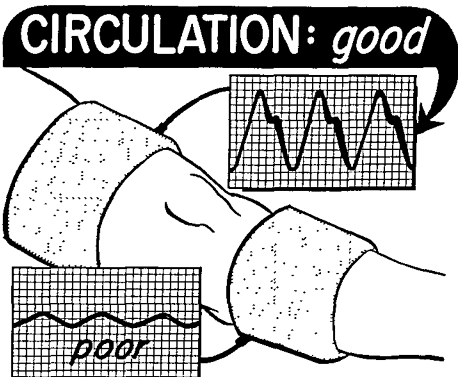


Figure 435. An above the knee amputation is probably necessary when the calf pulsates poorly while the thigh above the knee pulsates normally.

needs of the muscle are decreased during walking, however the patient's gait is altered (60). This procedure is seldom employed.

Nerve Crush

Crushing peripheral nerves or dividing them surgically may be employed in individual cases for relief of pain. The foot becomes

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